DOES NOT CIRCULATE

VOL. 50 OCTOBER, 1955 No. 4

AMERICAN HEART JOURNAL

AN INTERNATIONAL PUBLICATION FOR THE STUDY OF THE CIRCULATION

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Vol. 50, No. 4, October, 1955, American Heart Journal is published monthly, by The C. V. Mosby Company, 3207 Washington Avenue, St. Louis 3, Missouri, entered as second class matter January 23, 1917 at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Additional entry authorized at Jefferson City, Missouri. Subscription Price: United States, and its Possessions, per year $12.00; Canada $13.00; Foreign $13.50. Printed in the U. S. A.

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American Heart Journal

VOL. 50 OCTOBER, 1955 No. 4

Original Communications

EXPERIMENTAL PREVENTION OF SUDDEN DEATH FROM ACUTE CORONARY ARTERY OCCLUSION IN THE DOG

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BUFFALO, N. Y.

IT HAS been well documented that frequently the severe manifestations of acute coronary insufficiency and, on occasion, the sudden deaths of patients are out of proportion to the findings at necropsy. We have been impressed, as have others, with the young, apparently healthy individual who succumbs to his first "heart attack" within a matter of hours. Not infrequently such patients show at necropsy no occlusion of coronary arteries, no evidence of myocardial infarction, or a small vessel occlusion with a small area of infarction.[1-5] The immediate cause of death has been established by many investigators as ventricular fibrillation or ventricular standstill, the former being most common. The cause of the abnormalities of rhythm following acute coronary artery occlusion has been attributed to an irritable focus in the infarcted area from which arise ectopic stimuli resulting in disturbances in cardiac rhythm and frequently fatal ventricular fibrillation. Leroy and Snider[5] postulated that the sudden death of a patient with infarction of the myocardium is due to reflex coronary vasoconstriction, whose stimulus is the infarct, whose afferent pathway is the cardiosensory innervation, and whose efferent pathway is the vagus. The result of this reflex vasoconstriction, they felt, is fatal ventricular fibrillation.

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This study was supported in part by Grant H-1372 from the National Institutes of Health, United States Public Health Service.

Received for publication Feb. 11, 1955.

The authors are interested in trying to determine more about the mechanism and etiology of ventricular fibrillation in acute coronary occlusion and to investigate methods for its prevention. If fatal ventricular fibrillation could be prevented, then many cases of sudden death from acute myocardial infarction might be prevented.

Many experimental methods have been advocated to prevent the sudden death from acute coronary artery occlusion. The administration of various drugs[6-8] to increase the coronary blood flow or to decrease the occurrence of cardiac arrhythmia, especially fibrillation, has been used with some success. The experimental denervation of the heart[9,10] and, more specifically, of the coronary circulation[11] has lessened the incidence of sudden death in the experimental animal.

A review of the literature soon revealed a large spread in the expected mortality from acute occlusion of a major branch of the coronary arterial system in the dog. Mortality figures by various authors[9,12-15] have varied from 0 to 100 per cent. It was felt, therefore, that in order to obtain consistent results, a standardized technique was needed. This we have attempted to develop in our laboratory.

It was noted early in our experimentation and commented on by others in their investigations that in the immediate period following the acute occlusion, any somatic stimulation such as removal of a rib retractor, attempt to close a thoracic wound, or lifting the dog from the operating table would initiate an abnormality of cardiac rhythm and frequently result in fatal ventricular arrhythmias. Observations of this type raise an important question: Do all the so-called stimuli that may initiate abnormalities of cardiac rhythm in acute coronary artery occlusion arise from the irritable focus in the myocardium, or does the highly receptive irritable myocardium respond to extracorporeal stimuli?

Quinidine has long been known to be effective in the treatment of ventricular tachycardia and ventricular fibrillation.[16,17] Russek and Zohman[18] recently reported that one-half of the total mortality in so-called "good risk" cases of acute myocardial infarction occurs during the first 48 hours. They felt that it would appear to be a better rationale to routinely use quinidine rather than anticoagulant drugs during the first few days of the mild attack. Wegria and Nickerson[19] reported that in dogs, quinidine reduced the susceptibility to ventricular fibrillation. Smith and associates[20] observed that although animals receiving the drugs were susceptible to ventricular premature beats and ventricular tachycardia, they exhibited a diminished tendency toward development of fatal ventricular fibrillation. Mousset de Espanes[21] found no effect from quinidine in reducing the liability of the development of ventricular fibrillation following experimental coronary occlusion. Harris and associates[22] reported successful control of severe ventricular arrhythmias in the dog when quinidine gluconate was preceded with morphine sulfate.

Caution is necessary in attempting to apply the results in the study of animals to the problem of the use of quinidine in patients with coronary thrombosis. However, there is remarkable similarity between the symptoms exhibited by an animal dying of ventricular fibrillation and those of a man dying suddenly

of coronary occlusion. In both cases, there are cyanosis, pallor, venous congestion, gasping respiration, loss of pulse pressure, and a sudden loss of consciousness followed by death.

Various studies have shown that the sympathetic innervation of the heart plays an important role in the control of cardiac rhythm. Studies have shown that sympathetic nerve impulses to the heart and injected epinephrine can produce or facilitate the production of ectopic ventricular beats.[23-25] Excision of the upper thoracic sympathetic ganglion has been reported to diminish markedly the occurrence of premature beats and ventricular fibrillation during the immediate period of danger after sudden occlusion of a coronary artery[26-28] and reduce the over-all mortality.[10] Yodice[29] could not find any reduced mortality after sympathectomy. Harris and associates[30] divided the ectopic ventricular activity into three separate phases. He felt that upper thoracic sympathectomy, prior to occlusion of the anterior descending artery of the dog, reduces ectopic ventricular activity and the probability of ventricular fibrillation during the first ten-minute phase. It has also been reported that excision and removal of the stellate ganglia and adrenal glands greatly decrease the susceptibility of the heart to ventricular fibrillation following electric shock. Subcutaneous injection of adequate amounts of Adrenalin restores the normal response to the shock, and if greater quantities are injected in these or in normal animals, the danger of fatal ventricular fibrillation is greatly increased.[31] In order to try to obtain some of the answers involved in the prevention of ventricular fibrillation following acute coronary occlusion, the following experiments were devised.

EFFECT OF CORONARY LIGATION IN UNTREATED ANIMALS

Methods and Materials.—Adult mongrel dogs, weighing 25 pounds, plus or minus 5 pounds, were selected for study. The dogs, chosen at random as to sex, were acclimated to the kennel for a period of 2 weeks prior to use. All dogs were examined for gross evidence of disease and the state of nutrition, and were immunized against distemper on admission to the kennel.

The dogs were allowed nothing by mouth after 5:00 P.M. of the day prior to surgery. No preoperative medication in the form of atropine or morphine was administered. The animals were anesthetized intravenously with veterinarian Nembutal sodium, 30 mg. per kilogram of body weight. An endotracheal tube with inflatable cuff was passed and connected to an ether vaporizer and a respirator.* One hundred per cent oxygen was administered at controlled pressures, and rhythmical respirations were maintained by use of the Burns Valve.* Previous investigations in this laboratory by Dameron and Greene[32] have shown that this respirator gives adequate pulmonary ventilation and arterial oxygen saturation in open- or closed-chest procedures. They showed many advantages of the Burns Valve for anesthesia in intrathoracic surgery.

The animals were placed on their right side and the left chest prepared. An arterial cannula was placed in the carotid artery and attached to a U-type mercury recording manometer. An electrocardiogram was then obtained as

*Mine Safety Appliance Company, 201 N. Braddock Ave., Pittsburgh 8, Pa.

a base line, and the left chest was entered aseptically in the fourth intercostal space and the ribs spread. The left lung was partially deflated and packed off. The pericardium was exposed and incised longitudinally medially to the phrenic nerve. Care was taken not to injure the phrenic or vagus nerves. The tip of the left auricular appendage was grasped with a forcep and retracted laterally and superiorly. The epicardium and pericoronary fat in the region of the left coronary artery were incised, and the left coronary artery at its bifurcation to form the circumflex branch and the anterior descending branch was exposed. The anterior descending branch of the left coronary artery was carefully dissected free at its origin for a distance of approximately 1 cm. A No. 20 cotton ligature was passed around the artery with a ligature carrier, care being exercised not to include or damage the accompanying vein. The crushed portion of the auricular appendage was then ligated proximally, and all packs, instruments, and retractors were removed from the chest cavity. The left lung was re-expanded under positive pressure. A period of 5 minutes was allowed to elapse before any further intervention. Another electrocardiogram was then obtained, and the blood pressure was noted. The ligature was then tied snugly, occluding the artery. A drape was placed over the chest wound, and aeration was maintained by the respirator, using 100 per cent oxygen at 10 to 15 cm. mercury pressure. No attempt was made to close the thoracic wound, observe the heart, move or disturb the dog for a minimum of 30 minutes after acute ligation of the anterior descending branch of the left coronary artery. Electrocardiographic tracings were obtained at 5-minute intervals until termination of the acute experiment. If the animal survived the 30-minute period, the thoracic wound was then closed in layers and the chest aspirated. Following the conclusion of the operative procedure, the dog was not returned to his kennel until fully awake. No postoperative medication of any kind was administered except one intramuscular dose of 300,000 units of penicillin.

Electrocardiographic recordings were then obtained 24, 48, and 72 hours, and 1 and 2 weeks following the surgery. The surviving dogs were sacrificed at the end of 2 weeks. Complete autopsy, exclusive of the brain, was performed. The heart weight, size, and distribution of the infarct were noted. The thickness of the wall in the normal ventricular portion and in the infarcted area was noted as was the point of ligation. Sections were then obtained for histologic study. The remainder of the animal was examined for other abnormalities, particularly pulmonary lesions, which might have contributed to the death of the animal if he had not been sacrificed.

Results.—Twenty-six mongrel dogs were used in this series. Sudden death was considered to have occurred when the dog succumbed within 24 hours after ligation of the anterior descending branch of the left coronary artery above the first interventricular branch. Eleven of the twenty-six dogs died within 30 minutes of ligation from ventricular fibrillation. Five additional dogs died within the first 24 hours, making a total of sixteen dogs succumbing to sudden death following acute occlusion of the left anterior descending coronary artery. All of the surviving dogs were sacrificed after 2 weeks. Gross and microscopic

examination of the hearts of all dogs revealed a typical anterior wall infarct of the left ventricle. The point of occlusion of the anterior descending branch was found to vary no more than 5 mm. from its origin from the left coronary, and there were no ventricular branches proximal to the point of ligature. From gross and histologic evidence, the occlusion in all animals was complete. None of the animals died of ventricular standstill in the first 30 minutes. In the untreated group, 42 per cent died in 30 minutes, and a total of 62 per cent of the animals succumbed within the first 24 hours.

EFFECT OF QUINIDINE ON RESULTS OF CORONARY LIGATION

Experimental Procedure.—In the second phase of our studies on the experimental prevention of sudden death from acute coronary occlusion, quinidine hydrochloride was used. Except for slight modifications, the experimental technique already described was used. In addition, the left internal jugular vein was cannulated in the neck and the cannula connected to an infusion apparatus. Quinidine hydrochloride, diluted in normal saline, was infused intravenously beginning at the moment of occlusion of the vessel. The rate of flow was governed by the response of the dogs, blood pressure, pulse rate, and electrocardiographic observations. When evidence of tachycardia, runs, or numerous ventricular extrasystoles was noted, the rate of infusion was increased. When the rate of the pulse was slowing and fewer ventricular extrasystoles were seen, the rate of infusion was slowed. The total calculated dose of quinidine hydrochloride and saline was administered over a period not exceeding 45 minutes. The dose of quinidine hydrochloride was 15 mg. per kilogram of body weight diluted with normal saline, 18 ml. per kilogram of body weight.

Results.—Twenty-six mongrel dogs were studied in this manner. Eight dogs, or 31 per cent, died of ventricular fibrillation within 30 minutes after ligation of the anterior descending branch of the left coronary artery. An additional four dogs succumbed in the succeeding 24 hours. Thus twelve dogs, or 46 per cent, were classified as having undergone sudden death from acute coronary artery occlusion. The remaining fourteen dogs survived the initial 24-hour period.

EFFECTS OF BILATERAL THORACIC SYMPATHECTOMY ON RESULTS OF CORONARY LIGATION

Experimental Procedure.—Staged bilateral thoracic sympathetic ganglionectomies were performed on twenty-eight mongrel dogs followed by sudden occlusion of the anterior descending branch of the left coronary artery. The left sympathetic ganglionated chain was extirpated from T-1 through T-8. The thoracic wound was then closed in layers, the lung reinflated, and the thorax aspirated. Penicillin was administered intramuscularly daily following the surgery. Seven days later, the right chest was entered through the bed of the sixth rib, and the right sympathetic ganglionated chain was excised. On the seventh day following the right thoracic sympathectomy, the left chest was

again entered through the left fourth intercostal space and the anterior descending branch of the left coronary artery ligated as described previously.

Results.—Four dogs succumbed within 30 minutes of acute occlusion of the anterior descending branch of the left coronary artery. An additional seven dogs died in the succeeding 24 hours, or 39 per cent of the dogs succumbed suddenly from the acute occlusion of the coronary vessel. Seventeen, or 61 per cent, of the dogs survived the initial 24-hour period.

EFFECTS OF STELLATE GANGLION INJECTION ON RESULTS OF CORONARY LIGATION

Experimental Procedure.—In the fourth phase of our study, the effect of novocain injection into the left stellate ganglion was observed. Following ligation of the anterior descending coronary artery, using the procedure described previously, and taking no more time than was necessary to identify the stellate ganglion (usually no more than a matter of a minute), 1 c.c. of 1 per cent novocain was injected into the ganglion. The novocain was dissolved in a vital blue stain for easy identification. This procedure was performed on fifty mongrel dogs.

Results.—Six dogs succumbed within 30 minutes of acute occlusion of the anterior descending branch of the left coronary artery. An additional two dogs died within 24 hours. Forty-two, or 84 per cent, of the dogs survived the initial 24-hour period. None of the animals that developed ventricular fibrillation survived. It was observed during the procedure that ectopic ventricular beats were much less numerous during the first 30 minutes in this experiment than in the previous three procedures. In twenty-four animals there were no ectopic ventricular beats, and in fifteen animals there were only occasional ectopic ventricular beats observed. Three animals developed ventricular tachycardia at 10 and 15 minutes, but there were no ectopic ventricular beats observed at the end of the procedure. Of the forty-two survivors, the 24-hour electrocardiogram showed ventricular tachycardia in sixteen, frequent ectopic ventricular beats in seventeen, and no evidence of ectopic activity in nine.

DISCUSSION

The technique described in the surgical approach to experimental occlusion of the coronary artery in the dog is one that should give standardized results. It is felt that this is due to the use of the Burns Valve, the maintenance of adequate airway, precise placement of the ligature on the coronary artery, adequate expansion of the lungs, and the elimination of extracorporeal somatic stimuli.

From various experiments done, it can be concluded that the sympathetic innervation of the heart plays an important role in the control of cardiac rhythm. The spinal accelerator cells, located in the lateral horn of the upper thoracic segments of the spinal cord, connect with the inferior, middle, and superior cervical ganglia, and when stimulated, increase the heart rate via the sympathetic nervous system. Stimulations of the accelerator fibers, located in the inferior,

middle, and superior cardiac nerves, cause a rise of blood pressure and an increase both in the heart rate and force of contraction.

Despite considerable experimental work, there is no unanimity of opinion concerning the mechanism or importance of the reflex control of the coronary arteries. This is due in part to the technical difficulty of separating vasomotor effects and such factors as heart rate and blood pressure which also influence the coronary flow. Important vasomotor reflexes adapt the coronary flow to increased work of the heart. Such proprioceptive reflexes that originate in the heart and in great vessels produce coronary dilatation. This has been thought due to vagal inhibition. Anrep and Seigel[33] thought that vagal inhibition was the cause of such dilatation as proved by the fact that the effect was lost after vagotomy but not after stellate ganglionectomy. They felt that their experiments demonstrated the presence of vasoconstrictor fibers to the coronary blood vessels in the vagi and of vasodilator fibers in the sympathetic nerve. Greene[34,35] has studied these reflexes and has mentioned the universality with which stimulation in different parts of the body produces coronary dilatation.

From our studies and from those of others, it can be reasonably concluded that thoracic sympathectomy and procaine injection of the stellate ganglion protect the dog from ventricular fibrillation following coronary occlusion. We feel that the fatal stimulus from an extracorporeal source may be mediated predominantly over the cardiac sympathetic plexus arising from the cervical and thoracic sympathetic ganglia. When the heart is ischemic and irritable, it is apparently receptive to almost any type of stimulus.

Further studies in the prevention of sudden death from ventricular fibrillation following an acute coronary occlusion must be done, and further experiments are planned in our laboratory.

SUMMARY

A standardized procedure for the production of an acute coronary occlusion in the dog has been described. This method minimizes extracorporeal stimuli. The authors feel that this method offers a lower mortality than that expected from previous reports and can be utilized as a control study for further experimentation. We feel that this method gives a more accurate mortality rate directly from the coronary occlusion and that in no other published accounts have all of the factors, apart from occlusion and infarction, been taken into consideration in computing the mortality figures. In the control series, sixteen, or 62 per cent, of the twenty-six dogs died within the first 24 hours.

The effect of quinidine upon the mortality due to acute coronary occlusion in the dog was studied in twenty-six animals. Twelve, or 46 per cent, died within the first 24 hours.

The effect of bilateral thoracic sympathetic ganglionectomy upon the mortality due to acute coronary occlusion in the dog was studied in twenty-eight animals. Eleven, or 39 per cent, died within the first 24 hours. The effect of procaine injection of the left stellate ganglion upon the mortality due to acute

coronary occlusion in the dog was studied in fifty animals. Eight, or 16 per cent, died within the first 24 hours. It is concluded that thoracic sympathectomy and procaine injection of the left stellate ganglion protect the dog from ventricular fibrillation and death following coronary occlusion.

SUMMARIO IN INTERLINGUA

Le autores es interessate in le prevention de morte subite ab fibrillation ventricular post acute occlusion coronari. Illes describe un standardisate methodo pro le production de acute occlusion coronari in le can. Le methodo se distingue per le facto que illo involve un minimo de stimulos extracorporee durante le periodo quando le myocardio es receptivissime. Illo utilisa le valvula Burns que mantene un respiration rhythmic.

In le serie de controlo 38 pro cento del canes superviveva (i.e. 8 ex 26); con quinidina, 54 pro cento superviveva (i.e. 14 ex 26); con bilatere ganglionectomia sympathic thoracic, 61 pro cento (i.e. 17 ex 28). In 50 canes le sinistre ganglion stellate recipeva un injection de procaina con le resultato que 84 pro cento del gruppo superviveva.

Nos conclude que sympathectomia thoracic e injectiones in le ganglion stellate protege le can contra fibrillation ventricular post occlusion coronari. Nos opina que stimulos mortal effectuate per factores extracorporee es possibilemente mediate a un grado predominante per le plexo sympathic cardiac que se deriva ab le gangliones cervical e thoracic.

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THE ELECTROCARDIOGRAM IN CHRONIC CHAGASIC MYOCARDITIS

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THE fact that cardiac arrhythmias are strikingly frequent in patients with chronic chagasic myocarditis was noticed by Carlos Chagas from the beginning of the studies which led him to the discovery of the disease which bears his name.[6-8] Nothing can stress the importance of this prominent fact better than his own words: "Among the most interesting clinical expressions of the Schizotrypanosis, due to its great medical and pathogenic importance, are the disturbances of the cardiac rhythm, determined by the localization of lesions produced by the Schizotrypanum in the myocardium. This phenomenon, very common in the geographical zone studied, its frequency being impressive and certainly never observed outside of this epidemiologic condition, had awakened our attention from the beginning of our clinical studies . . ." (our translation). It is remarkable that the existence of ectopic beats, of nodal rhythm and, especially, of different degrees of A-V block was recognized and carefully described by Chagas as early as 1910-1911, on the basis of simple clinical examination or with the aid of some more or less cumbersome methods for the study of the mechanical activity of the heart.

Many years later, when the electrocardiograph became a more widely used instrument for the exploration of cardiac patients, the simple standard leads permitted also the recognition of the very high incidence of abnormalities of the intraventricular conduction and of the T wave,[10] which are also distinctive features of the disease. But it was not until the introduction of the multiple unipolar leads as applied to the study of large groups of patients with chronic chagasic myocarditis that the electrocardiogram demonstrated its considerable value for the diagnosis of the disease.[11,15,17] As patients with the chronic form of Chagas' disease may or may not have myocardial involvement, the electrocardiogram is, in many cases, the only way of recognizing the presence of myocardial lesions, that is to say chronic myocarditis, in cases in which the chagasic etiology has been previously ascertained.

Up to now, the larger groups of cases of chronic chagasic myocarditis selected for electrocardiographic study were collected through epidemiologic investigations in highly endemic areas,[11,15,17,33] comprising unselected groups

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Received for publication Feb. 25, 1955.

of the general population. In this paper, we shall present and discuss the fundamental electrocardiographic findings in the first 130 cases of the chronic form of Chagas' disease studied in the "Pabellón de Cardiología Luis H. Inchauspe, Policlínico Ramos Mejía, Buenos Aires" in the last five years. A group of unselected cases studied in an epidemiologic investigation in Brazil by Dias and co-workers[11] will be used for comparative purposes. Special consideration shall be given to the evaluation of each isolated electrocardiographic abnormality and to the different ways in which they can combine, giving place to useful diagnostic associations.

MATERIAL

Electrocardiograms (381) were recorded in 130 cases of the chronic form of Chagas' disease. The criteria for that diagnosis were (a) a clinical history strongly suggestive of the possibility of having acquired the disease. That means that the patient was living or had lived for a long period of time in a well-recognized endemic zone, was usually able to describe or recognize in appropriate photographs the transmitting insect (*Triatoma infestans*)* and in most of the cases he remembered having been bitten. We shall refer to (a) as a positive epidemiologic history. (b) An intensely positive serologic test of fixation of the serum complement with antigen prepared with a culture of *Schizotrypanum cruzi*. This test is a modification of the diagnostic procedure originally developed by Guerreiro and Machado,[15] and we shall refer to it by the name of those authors. In seven cases out of thirty-nine in which it was done, the xenodiagnosis† was positive.

The diagnosis of chronic chagasic myocarditis was made when clinical, radiologic and/or especially electrocardiographic signs of myocardial involvement were present, following previously established criteria.[11] For this paper, the electrocardiographic criteria have been a priori accepted as valid, but they will be discussed in detail in the following pages. On the other hand, the absence of any clinical evidence of rheumatic, syphilitic, congenital, arteriosclerotic, hypertensive, etc., heart disease in most of the cases, supported the diagnosis of primary myocardial disease. The cases in which some other etiologic factor was present were especially considered[41] and will be discussed in connection with each electrocardiographic abnormality for which they could have been also responsible. In five cases in which an autopsy was performed, the histologic study demonstrated a chronic disseminated myocarditis with the characteristics usually ascribed to the disease; but we were not able to prove the presence of parasites in the myocardium.

Of the 130 cases, sixty-four were men and sixty-six women, and the age distribution was as follows: 10 to 20 years, six cases; 21 to 30 years, nine cases;

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*In Argentina, Uruguay, Chile, Paraguay, and Bolivia the usual popular name for the insect which transmits the disease is "vinchuca." Of the many varieties of triatomids, the most important in those countries is *Triatoma infestans*.

†The xenodiagnosis is a form of hemoculture performed in the body of the insect which transmits the disease. The insect is allowed to bite the suspected patient, then its feces, and finally its intestine, are examined for the presence of the parasite at variable intervals.[40]

31 to 40 years, twenty-seven cases; 41 to 50 years, thirty-five cases; 51 to 60 years, thirty cases; 61 to 70 years, fifteen cases: and 71 to 80 years, eight cases (average age, 47 years).

RESULTS

In Table I the fundamental findings and their percentage incidence are shown, compared with 183 cases reported by Dias and co-workers,[11] from an epidemiologic study in Bambui, Minas Gerais, Brazil. In Figs. 1 to 19, examples of the most frequent and characteristic abnormalities are given, with a short summary of the corresponding clinical facts.

TABLE I. ECG IN THE CHRONIC FORM OF CHAGAS' DISEASE

	BUENOS AIRES (130 CASES)		BAMBUI (183 CASES)	
	CASES	PER CENT	CASES	PER CENT
Normal ECG	17	13.07	93	51.8
Abnormal ECG	113	86.97	90	49.2
	113 ABNORMAL ECG		90 ABNORMAL ECG	
	CASES	PER CENT	CASES	PER CENT
1. Right B. B. B.	63	55.7	35	38.8
2. Left B. B. B.	3	2.6	0	
3. Partial A-V block	8	7.0	35	38.8
4. Complete A-V block	5	4.4	9	10.0
5. Low voltage, notching, and slurring of the QRS	17	13.0	6	6.6
6. T-wave abnormalities	48	42.4	9	10.0
7. Left ventr. enlarg.	25	22.1	0	
8. P-wave abnormalities	26	23.0	5	5.5
9. Ventric. extrasystoles	61	53.9	24	26.6
10. Auric. extrasystoles	14	12.3	6	6.6
11. Auric. fibrillation	14	12.3	4	4.4
12. Auric. flutter	5	4.4	0	
13. Supraventr. tachycardia	1	0.9	1	1.1
14. Ventric. tachycardia	7	6.2	3	3.3

Table I shows that the same wide variety of electrocardiographic abnormalities was present in ours and in Dias and co-workers' patients. The same fact is also disclosed by all the reported groups of cases in which the diagnosis was made on a similar basis,[3,5,16,18,24,29-31,33-35] and serves to emphasize that all the same types of electrocardiographic alterations are present in chronic chagasic myocarditis, even when the human material is selected under different circumstances. It should not be surprising if this would only happen in cases selected in cardiologic departments, where so often the electrocardiographic abnormalities themselves are the most important diagnostic findings. (Better proof that these abnormalities are specifically related to Chagas' disease is the fact that they are also present in the material of epidemiologic studies, as exemplified

by the patients of Dias and associates. In these epidemiologic studies, the selection of the patients was made on the basis of a positive epidemiologic history and a positive Guerreiro-Machado test. When in the same region, groups of people with negative Guerreiro-Machado test were studied, practically no electrocardiographic abnormalities were observed.[18]

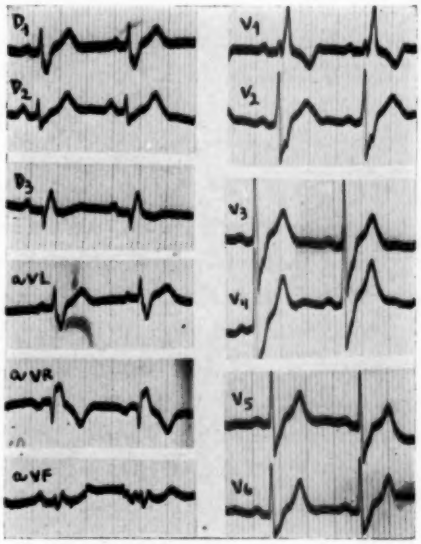


Fig. 1.—Asymptomatic 58-year-old man. Uncomplicated right bundle branch block. Left ventricular enlargement (++). Positive xenodiagnosis.

While the electrocardiogram was abnormal in 86.9 per cent of our cases of chronic chagasic myocarditis, only 49.2 per cent of the patients of Dias and co-workers showed an abnormal tracing. The difference is explained by the manner in which both groups of cases were selected. In the study made by Dias and co-workers, a sample of the general population was investigated, consequently including many individuals in whom myocardial involvement had not yet developed. On the contrary, our group represents a typical sample of patients coming to a clinic exclusively devoted to the management of cardiac diseases. In most instances, our patients came because they already presented symptoms and signs, which they themselves or the general practitioners who sent them to us, thought to be of cardiac origin. The same situation explains the differences concerning each electrocardiographic abnormality, for the most important of them (right bundle branch block, T-wave changes, ectopic beats, auricular fibrillation, etc.) were much more frequent in our group of cases, which definitely represents a more advanced stage of the disease. The differences concerning A-V block and left ventricular enlargement will be fully analyzed under the corresponding headings. Laranja,[17] commenting on the electrocardiographic abnormalities studied in Bambui, pointed out that those results had to be considered as an expression of an epidemiologic investigation and predicted that the per cent incidences would be different in cases studied in cardiologic services.

SPECIFIC ELECTROCARDIOGRAPHIC ABNORMALITIES

1. *Right Bundle Branch Block.*—The extraordinary high incidence of right bundle branch block in chronic chagasic myocarditis is today a well-known and accepted fact. It was present in 55.7 per cent of our abnormal electrocardiograms, and similarly high incidences (30 to 50 per cent) have also been reported in all the published large groups of cases.[3,5,11,16,18,24,29-31,33] If we disregard some congenital anomalies, for instance interatrial septal defects, chronic chagasic myocarditis is the disease in which right bundle branch block appears with the highest incidence. Without other typical findings present, this alone would be enough to give to the disease its most peculiar character.

To determine what the importance of Chagas' disease would be in the general incidence of right bundle branch block, we studied the etiologic factors in 100 cases of this conduction disturbance (Table II). Notwithstanding that Chagas' disease is present in no more than 1.5 to 3.0 per cent of the patients who are admitted to our service, its incidence in the hundred cases of right bundle branch block was 16 per cent. Table III shows how the incidence of Chagas' disease became even greater when only cases of right bundle branch block accompanied by T-wave abnormalities were considered. These results strongly suggest the possibility that in endemic areas, where Chagas' disease can be the most important etiologic cause of heart disease,[28] the great majority of cases of right bundle branch block must be of chagasic origin.

From the beginning of our studies on Chagas' disease it became apparent that associated electrocardiographic abnormalities are more frequent in chagasic than in nonchagasic cases of right bundle branch block. To prove whether or not these initial observations were correct, a comparative study was made between sixty-three chagasic and sixty-five nonchagasic cases of right bundle branch block. The results summarized in Table IV show that especially T-wave abnormalities and ventricular ectopic beats were far more frequent in the chagasic group. At least some type of associated abnormality was present in 76.2 per cent of the chagasic and in only 44.7 per cent of the nonchagasic group. We shall later elaborate on the diagnostic value of these combinations of electrocardiographic abnormalities.

Impressed by the great frequency of pronounced left-axis deviation in chagasic right bundle branch block, we also studied the direction of the mean electrical axis ($\hat{A}_{QRS}$) in both groups of cases, determined by simple examination of the standard and unipolar extremity leads. The error involved in this procedure is usually no greater than 15 degrees.[45] In thirty-three cases of the chagasic group (52.5 per cent) the $\hat{A}_{QRS}$ was between 0 and -100 degrees. In nine of these thirty-three cases, arterial hypertension was also present. There was no great difference regarding the distribution of the $\hat{A}_{QRS}$ in the nonchagasic group, in which 47.5 per cent (31 cases) had an $\hat{A}_{QRS}$ between 0 and -100 degrees, which is not surprising, as the most common causes for left ventricular hypertrophy were present in that group, arterial hypertension being observed in twenty-five of the thirty-one cases. We believe that this type of right bundle

branch block accompanied by pronounced left-axis deviation indicates in most of the cases the presence of left ventricular enlargement, particularly when the $\hat{A}_{QRS}$ reaches −30 degrees or more to the left. In fact, left ventricular enlargement was confirmed by fluoroscopy in both the chagasic and nonchagasic cases showing an $\hat{A}_{QRS}$ between 0 and −100 degrees. Our observations also support Barros'[3] statement that in cases of chagasic right bundle branch block in which there is no left-axis deviation, the clinical condition of the patient is less severe than when pronounced left-axis deviation is present.

TABLE II. ETIOLOGIES AND TYPES OF HEART DISEASE IN 100 CASES OF RIGHT BUNDLE BRANCH BLOCK

	CASES	PER CENT
Arterial hypert.	37	37
Pulmonary disease	17	17
Chagas' disease	16	16
Valvular disease	16	16
Arteriosclerot. heart dis.	15	15
Congenital heart disease	6	6
Constrictive pericarditis	1	1
No heart disease	5	5
Unknown etiologies	6	6

TABLE III. ETIOLOGIES AND TYPES OF HEART DISEASE IN 34 CASES OF RIGHT BUNDLE BRANCH BLOCK ACCOMPANIED BY ABNORMAL T WAVES

	CASES	PER CENT
Arterial hypert.	12	35.29
Chagas' disease	9	26.47
Valvular heart disease	7	20.58
Arteriosclerot. heart dis.	6	17.64
Pulmonary disease	3	8.82
Congenital heart disease	1	2.94
Constrictive pericarditis	1	2.94

TABLE IV. ASSOCIATED ELECTROCARDIOGRAPHIC ABNORMALITIES IN 63 CASES OF CHAGASIC AND 65 OF NONCHAGASIC RIGHT BUNDLE BRANCH BLOCK

	CHAGASIC CASES		NONCHAGASIC CASES	
	CASES	PER CENT	CASES	PER CENT
Uncomplicated R.B.B.B.	15	28.8	36	55.3
R.B.B.B. T-wave abnormalities	30	47.6	17	26.1
R.B.B.B. ventr. extr.	31	49.2	18	27.6
R.B.B.B. T-wave abnormalities, ventr. extr.	20	31.7	9	13.8
R.B.B.B. other abnormalities (auric. fibr., left ventr. enlarge., A-V block, etc.).	36	57.1	28	43.0

Among the cases of chagasic right bundle branch block with left-axis deviation it was rather common to find tracings characterized by very small or even absent S waves in Lead I and very deep S waves in Leads II and III (Figs. 2 and 3), of the type that can simulate left bundle branch block when precordial leads are not taken.* Its high incidence has been also reported in the studies made in Bambui, and Barros[3] emphasized the presence of very deep S waves

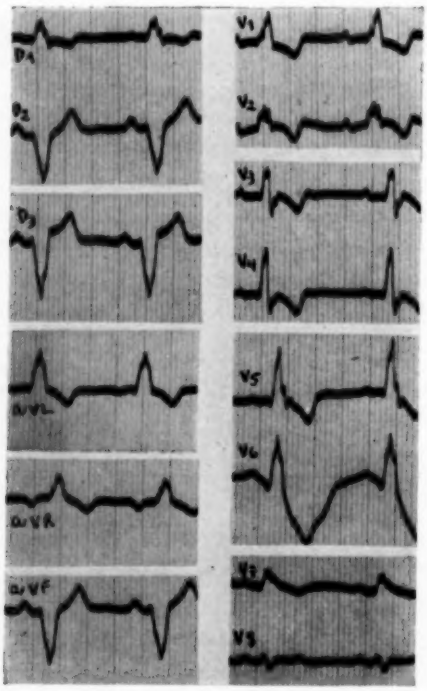


Fig. 2.

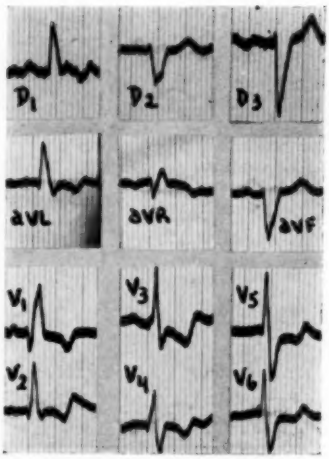


Fig. 3.

Fig. 2.—49-year-old man in advanced heart failure. Right bundle branch block with pronounced left-axis deviation and very small S wave in Lead I (Bayley's Type IV, which can simulate left bundle branch block in the standard leads). The notching and slurring of the R waves in left precordial leads with a delayed intrinsicoid deflection suggest left ventricular enlargement. Fluoroscopy strongly suggests posterolateral ventricular aneurysm. In other tracings, auricular and ventricular extrasystoles and short bouts of ventricular tachycardia. This patient was followed during two years.

Fig. 3.—50-year-old woman in severe heart failure and with pronounced heart enlargement, followed during two and one-half years. Right bundle branch block with pronounced left-axis deviation with very small S wave in Lead I (Bayley's Type IV which can simulate left bundle branch block in the standard leads). The S-T-T changes may be due to digitalis. In other tracings, frequent ventricular extrasystoles.

in Leads II and III in 80 per cent of eighteen cases of chagasic right bundle branch block. According to Laranja and associates,[16] this type of electrocardiogram would indicate a vertical heart with pronounced clockwise rotation produced by right ventricular dilatation. Similarly, Barker[2] accounts for this type of tracing assuming the existence of a vertical electrocardiographic position,

*Very recently four electrocardiograms showing this type of right bundle branch with pronounced left-axis deviation were reported by Richman and Wolff.[32] The vectorcardiograms of the four patients were considered as indicating that left and not right bundle branch block was the fundamental underlying condition. The fact that this type of tracing is so frequent in chronic chagasic myocarditis is an indirect evidence that it really represents right and not left bundle branch block.

with aV_L recording the potential variations of the right ventricular surface (like V_1) and aV_F recording the potential variations of the left ventricular surface (like V_5-V_6). We do not believe this explanation is right, at least for the majority of the cases in which that pattern is present, and we would instead ascribe it to a horizontal position in a heart with left ventricular enlargement. In fact, we consider this type of tracing, which belongs to Group IV of Bayley's[4] classification, simply as an exaggeration of those already mentioned as accompanied by pronounced left-axis deviation. Thus they are likely too to be associated with more or less pronounced left (and not right) ventricular enlargement. Lepeschkin[19] refers to the high incidence of left ventricular hypertrophy in patients with this type of tracing. In cases of right bundle branch block with predominant left ventricular hypertrophy, aV_L may have a predominant positive QRS complex (qR or R), in some ways similar to the pattern of the right precordial leads, without this being an evidence that the left arm is facing the right side of the interventricular septum or the right ventricle. It was demonstrated by cases of this type, in which right bundle branch block was intermittent or transient[44] that the QRS complex in aV_L showed practically the same configuration whether right bundle branch block or normal intraventricular conduction were present, proving that the electrocardiographic position of the heart can be entirely misleading under those conditions.

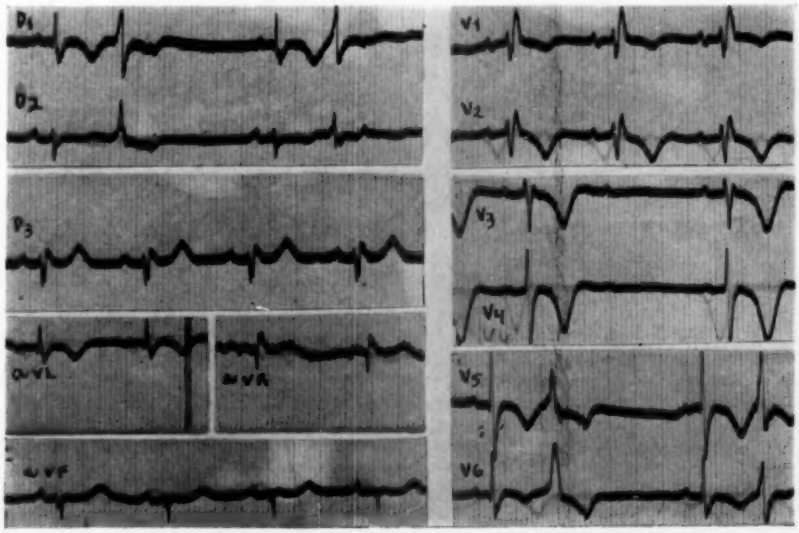


Fig. 4.—50-year-old woman with moderate heart failure and slightly enlarged heart. Right bundle branch block, primary T-wave changes, and frequent ventricular extrasystoles of two different shapes, sometimes as bigeminal rhythm. On some occasions, second degree A-V block (V_3-V_4). See the typical coronary aspect of the negative T waves in the precordial leads and the reciprocal changes in Leads I and III. The tracing was unmodified 30 days later. This electrocardiogram shows the most characteristic association of abnormalities in chronic chagasic myocarditis.

One of the most significant problems confronting the cardiologist in the presence of a patient having the chronic form of Chagas' disease is the diagnostic value to be attached to a right bundle branch block pattern. In other

words, to what extent is one justified in making the diagnosis of chronic chagasic myocarditis in a patient with the chronic form of Chagas' disease whose electrocardiogram shows right bundle branch block? The question arises from the now well-known fact that right bundle branch block, either complete or incomplete, may occur in clinically normal persons. It is then possible, for a given case of chronic form of Chagas' disease, to have right bundle branch block as an unrelated condition. In this case, right bundle branch block would not indicate the presence of myocardial involvement, and the diagnosis of chronic chagasic myocarditis should not be made.

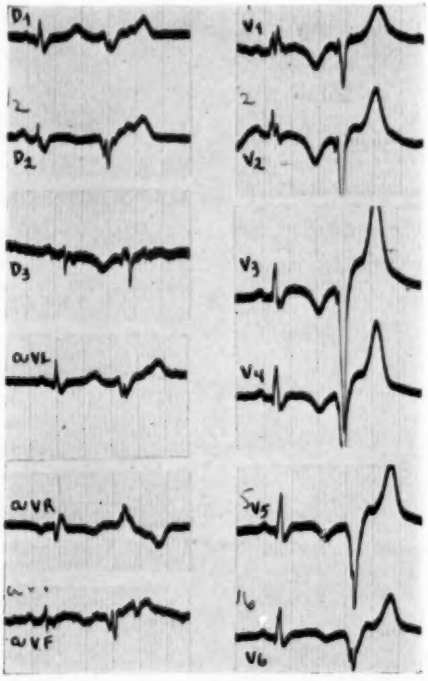


Fig. 5.—43-year-old woman, without any cardiovascular complaints. She was admitted to the hospital because of gall bladder disease and the surgeon asked for cardiac consultation because of her arrhythmic pulse. Right bundle branch block, primary T-wave changes, and bigeminal rhythm due to ventricular extrasystoles. Notice also in this case the "coronary" aspect of the T waves in all the precordial Leads, aV_F, II, and III, indicating extensive subepicardic myocardial involvement of the anterior and posterior aspects of the heart. A xenodiagnosis was positive. In spite of all this, she underwent a cholecystectomy with perfect tolerance.

The evaluation of the problem must take into consideration whether or not the right bundle branch block is associated with other electrocardiographic abnormalities, in other words, whether it is a complicated or uncomplicated case of right bundle branch block.

Associated electrocardiographic abnormalities were present in forty-eight and absent in fifteen of our sixty-three cases of chagasic right bundle branch block. In forty-five of the forty-eight complicated cases of right bundle branch block, the associated abnormalities (primary T-wave changes, ventricular extrasystoles, left ventricular hypertrophy, A-V block, auricular fibrillation, etc.), were more than enough to assume safely the existence of important myocardial

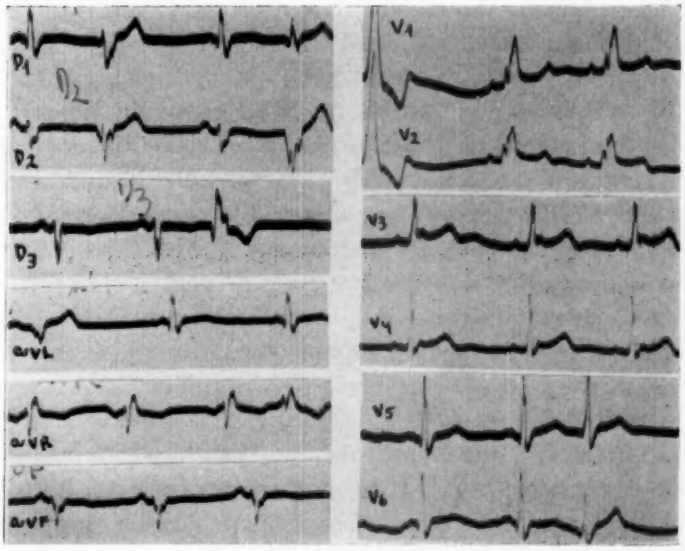


Fig. 6.—68-year-old man, with palpitations as the only complaint. Admitted to the hospital because of prostatic adenoma, he was also sent to us because of his arrhythmic pulse. Right bundle branch block with pronounced left-axis deviation. The flattened T waves in Leads I and V_6 are considered as definite evidence of myocardial damage in the presence of right bundle branch block. Very frequent ventricular extrasystoles of two different shapes. A xenodiagnosis was positive. A resection of his prostatic adenoma was done and perfectly well tolerated. This case and the one of Fig. 5 illustrate how sometimes patients with chronic chagasic myocarditis, even with parasites demonstrable in circulating blood, may lead practically normal lives.

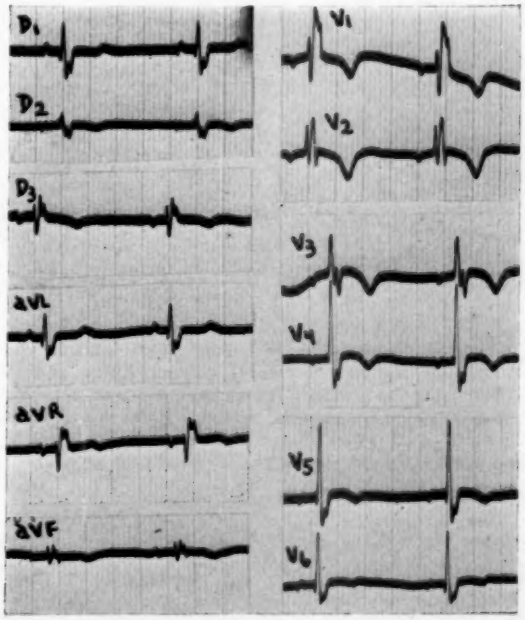


Fig. 7.—48-year-old man, asymptomatic, with a slightly enlarged heart. Right bundle branch block and primary T-wave changes indicating an extensive subepicardic myocardial involvement of the anterior and posterior aspects of the heart. The diphasic P waves in Leads II, III, aV_R and aV_F probably indicate an ectopic origin of the pacemaker. Five other tracings taken during one and one-half years were exactly the same and no extrasystoles were observed in many clinical examinations during the same period. However, after a short exercise he developed frequent ventricular ectopic beats, bigeminal rhythm, auricular extrasystoles, and a short period of A-V dissociation with interference, due to a slow rate ventricular ectopic rhythm.

involvement, according to the most common criteria utilized in clinical electrocardiography. We are well aware of the fact that it is possible to find some of these abnormalities, for instance T-wave changes, ventricular extrasystoles, some degree of A-V block, and auricular fibrillation in normal people. But it would be hard to believe that, when one or more of them are present in the same electrocardiogram, together with right bundle branch block, and in a patient with a chronic disease well known as able to produce myocardial lesions, they would mean simple functional phenomena. The three cases in which the only associated abnormality was the presence of ventricular ectopic beats were also considered as having myocardial involvement, because the extrasystoles were very frequent, in every clinical or electrocardiographic examination and, especially, because they showed at least two or more different configurations. This type of ventricular extrasystole is only rarely observed in normal people, and its association with right bundle branch block was considered as an impressive evidence of myocardial involvement particularly in patients of this type. Thus in the forty-eight cases of complicated right bundle branch block, the associated electrocardiographic abnormalities adequately fulfilled standard criteria for assuming the presence of more or less severe myocardial involvement, that is to say, the existence of chronic chagasic myocarditis.

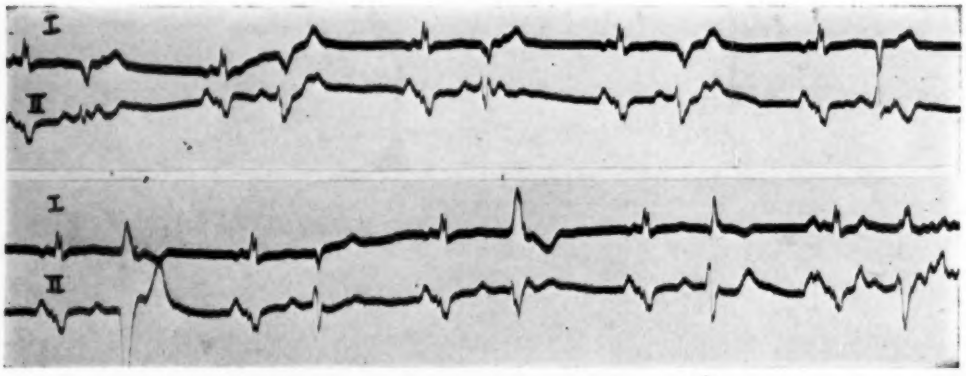


Fig. 8.—57-year-old woman, with moderate degree of heart failure. A continuous strip of Leads I and II shows bigeminal rhythm due to ventricular extrasystoles. Notice how the morphology of every ectopic beat is different from the others (this patient did not take digitalis). Also right bundle branch block, negative T waves in left precordial leads, left intraventricular conduction disturbance and abnormal P waves. In spite of all these abnormalities, this woman was leading a practically normal life and had been considered previously simply as a "nervous" patient.

Of the fifteen cases in which right bundle branch block was the only electrocardiographic abnormality, in six the heart was moderately enlarged at fluoroscopy. In the remaining nine cases, no other clinical or radiologic abnormalities could be demonstrated. So in only nine out of the sixty-three cases, right bundle branch block was the only evidence of possible myocardial involvement. If we assume that in all these nine cases right bundle branch block was a superimposed and unrelated fact of whatever origin, that would mean that in 14.2 per cent of our cases of right bundle branch block the diag-

nosis of chronic chagasic myocarditis could have been insufficiently supported. However, we still believe that most of those nine cases did really have chronic myocarditis. Even accepting that the diagnosis could be erroneous in some of them, this error will be less than if we assume the opposite position, that of rejecting the diagnosis because of the absence of more conspicuous signs of myocardial involvement. It is clear that, in the group of patients under discussion, right bundle branch block has more chances to be of chagasic origin than to belong to the group of normal people who show that conduction disturbance (Table II).

We have just discussed that associated electrocardiographic abnormalities in tracings with right bundle branch block are a valuable sign in the diagnosis of chronic chagasic myocarditis. This is especially true for primary T-wave changes and ventricular ectopic beats, which therefore warrant here a more intimate analysis. Concerning the T-wave abnormalities, it is important to make clear what we considered as primary T-wave changes in the presence of right bundle branch block.

In former papers[37,38] one of us has shown that in uncomplicated right bundle branch block, the T wave must be positive in leads facing the left ventricle, negative in aV_R, and can be positive, negative, diphasic, or isoelectric in right precordial leads. Right bundle branch block is in some way a partial security for the T wave keeping the same polarity as in the normal electrocardiogram, in left precordial leads, aV_R and Lead I. So inverted T waves in left precordial leads and Lead I and positive T waves in aV_R are definitely abnormal. Moreover, as right bundle branch block tends to make the T wave more positive in left precordial leads and in Lead I and more negative in aV_R, than they normally are, low-voltage T waves in those leads already indicate some myocardial abnormality. Empirically based observations indicate that negative T waves deeper than 1 millivolt in right precordial leads must also be considered as abnormal.[12]

If we compare the type of T-wave abnormality in the chagasic and nonchagasic cases of right bundle branch block, a definite difference is evident between both groups. Whereas in the chagasic group the T waves were almost invariably of the so-called ischemic or coronary type (Figs. 4, 5, and 7), in the nonchagasic group they were in most instances of the type which usually characterizes "left ventricular strain" or digitalis effect. The few nonchagasic cases in which abnormal T waves were also of the ischemic type were accompanied by QRS changes typical of myocardial infarction.

Concerning ventricular ectopic beats associated with right bundle branch block, they were rather infrequent and almost always of unifocal origin in the nonchagasic group, whereas in the majority of the chagasic cases, they were remarkably numerous, almost permanent and of multiform configuration in most of the cases.

Less valuable findings in chagasic right bundle branch block included pronounced left-axis deviation (in the absence of any disease capable of producing left ventricular hypertrophy, this can also be an indirect evidence of the chagasic etiology of the right bundle branch block pattern, in zones where the disease

is endemic), auricular fibrillation and other more or less complex arrhythmias, low voltage of the QRS complex, etc. But within certain limits the probability of chagasic origin was the more likely as the more associated electrocardiographic abnormalities were present.

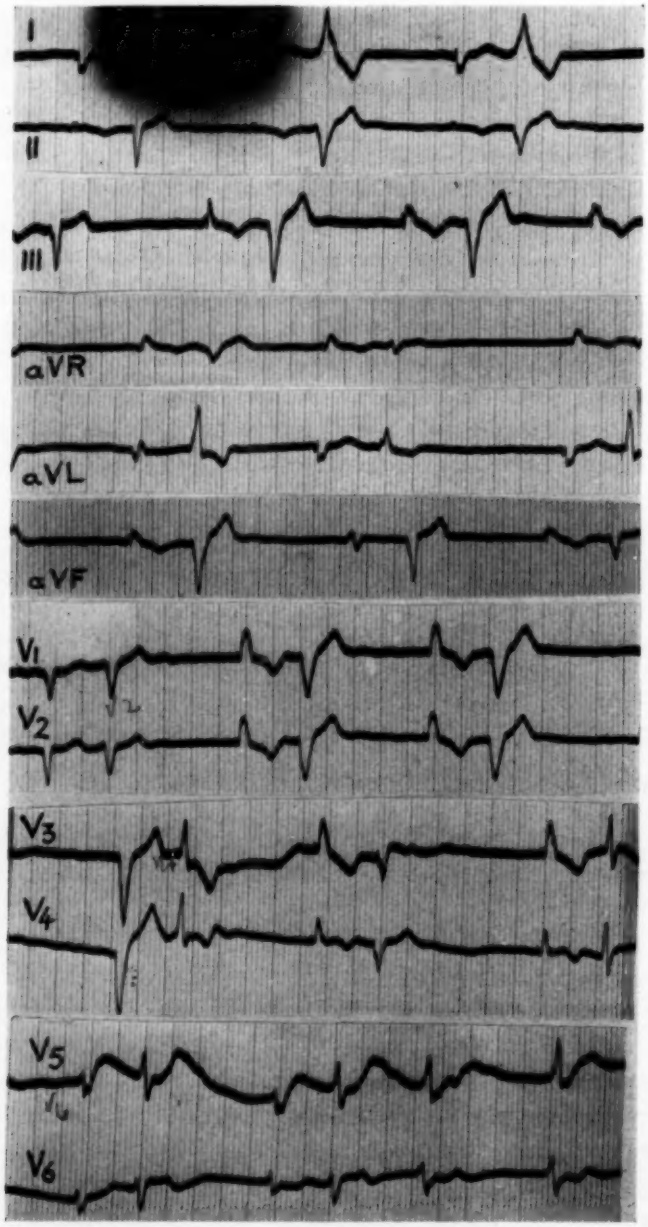


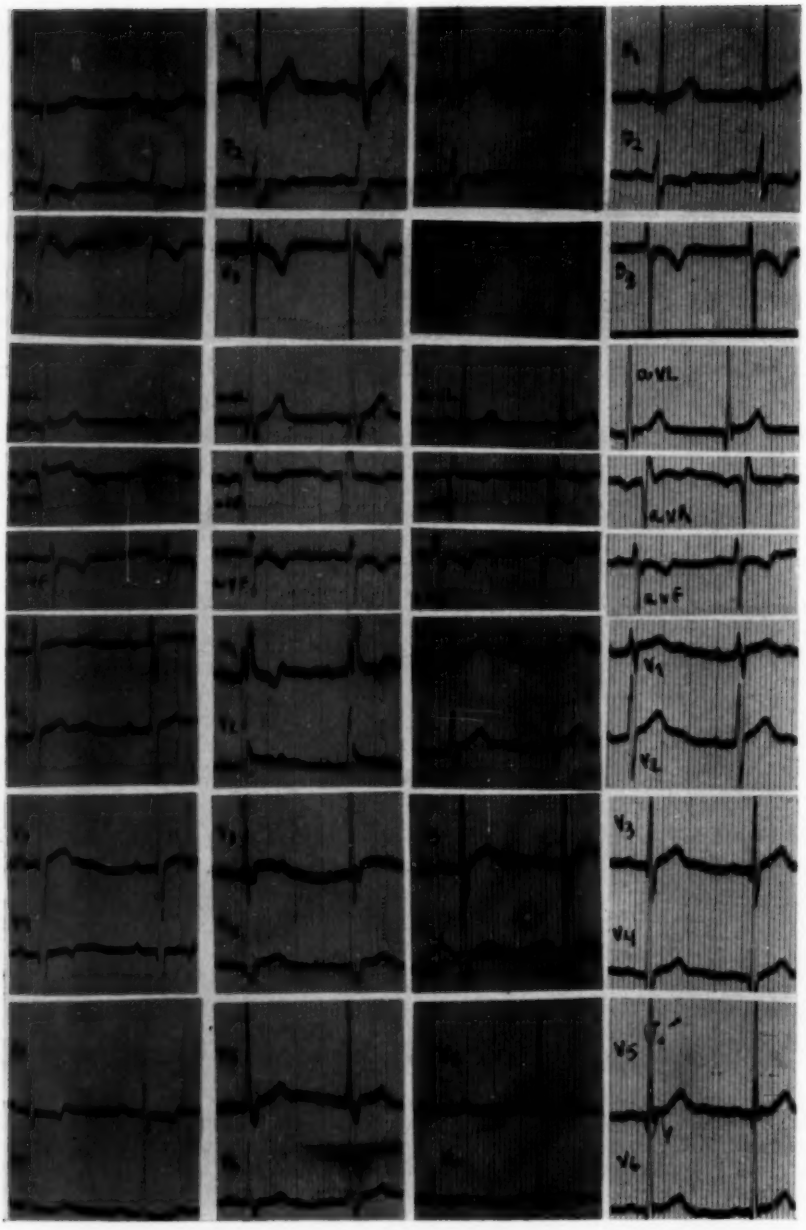
Fig. 9*A*.—48-year-old woman with very severe heart failure, was followed during 21 months until her death, which occurred while she was sleeping. The autopsy revealed the presence of very severe and extensive myocardial lesions and subacute pericardial involvement with a massive serohemorrhagic effusion (1,500 c.c. of fluid). Auricular fibrillation, right bundle branch block, and multiple and polymorphous ventricular extrasystoles and escaped beats. The second beat in Lead III probably represents a lesser degree of right bundle branch block.

In our experience, right bundle branch block with primary T-wave changes of the ischemic type and frequent and multiform ventricular extrasystoles were the most valuable diagnostic association of electrocardiographic signs. We do not intend to say that this electrocardiographic pattern is pathognomonic or indicates invariably the presence of chronic chagasic myocarditis, and we certainly realize that it may also be present for instance in cases of coronary heart disease. It is not exceptional to observe the association of right bundle branch block with primary T-wave changes in coronary heart disease, without QRS changes diagnostic of myocardial infarction, and there is no reason why in the same patient ventricular ectopic beats could not also be present. But when these ectopic beats are very frequent and polymorphous, we shall be facing a triple association of facts, which is certainly frequent in Chagas' disease but not so in coronary disease. In the last five years, over 5,000 electrocardiograms were examined in our electrocardiographic department, and in every case in which this type of tracing was observed, further clinical and serologic studies could demonstrate the existence of chronic chagasic myocarditis.*

Fig. 9*B*.—This figure illustrates a multitudinous variety of ectopic beats. Only the fourth, sixth, eighth, and twelfth beats in the upper strip and the second beat in the lower strip are of supraventricular origin. This type of tracing was the rule during the last 40 days of her life. She was under digitalis medication the whole time.

Contrasting with the very high incidence of right bundle branch block, left bundle branch block was only present in 2 per cent of our cases with abnormal electrocardiogram. The same fact is disclosed by most of the previously reported cases, and experimental chagasic myocarditis in the dog was demonstrated to be likewise associated with the production of right and not left bundle branch block.[16,27]

***There was only one exception to that, a 30-year-old woman, with moderate heart enlargement, and a positive epidemiologic history. In spite of three negative Guerreiro-Machado tests, the clinical history, the type of electrocardiographic abnormalities, and the absence of any other etiology strongly suggested the possibility of chronic chagasic myocarditis. This case has been discussed elsewhere[42] as an example of chronic chagasic myocarditis with negative serologic tests.**



A. *B.* *C.* *D.*

Fig. 10.—31-year-old man. He was first admitted with severe congestive heart failure and pronounced heart enlargement. By that time Aug. 5, 1949, *A*, typical pattern of left ventricular enlargement, with very high voltage of the QRS, pronounced left-axis deviation and characteristic S-T-T changes in left precordial leads. A month later Sept. 8, 1949, *B*, when he was compensated and the heart recuperated its normal size, right bundle branch block. In successive tracings the degree of right bundle branch block diminished, *C*, Sept. 15, 1949, until it almost disappeared, *D*, Sept. 30, 1949. Four years later he was completely asymptomatic, although he had for a long time abandoned any medication, but his electrocardiogram showed complete right bundle branch block (as in *B*) and the T waves were flat or inverted in left precordial leads. This case illustrates a subacute episode during the chronic process of the disease.

No satisfactory explanation has as yet been advanced for that extraordinary difference in the frequency of electrocardiographic involvement of the right and left branches of the bundle of His. Dias and co-workers[11] suggested the three following possible interpretations:

(a) Right bundle branch block would be more frequent due to the predominance of right rather than left heart failure in the clinical course of the disease. This does not account for the great number of cases in which right bundle branch block is observed in the absence of heart failure.

(b) According to an old concept advanced by Wenckebach, whenever there are diffuse and simultaneous lesions in both ventricles, the right ventricle would be more prone to become insufficient or to give place to clinical symptoms, owing to its natural weakness compared with the greater anatomic and physiologic development of the left ventricle. If it is true that myocardial damage in Chagas' disease is usually diffuse, the process including both ventricles, most anatomic reports are consistent with a greater intensity of the lesions in the left than in the right ventricle. We have also recently insisted[1] on the fact that from a radiologic and electrocardiographic point of view, the left rather than the right ventricle seems to be more affected, which especially holds true in the less advanced forms of the disease. On the other hand, even if the above concept applies to the function of the right versus the left ventricle, this does not signify that the same will be true for the function of the right versus the left branch of the bundle of His. We believe this explanation can be disregarded.

(c) The longer undivided course of the right bundle branch on the right surface of the septum does make it anatomically more vulnerable than the left branch which starts to branch off early in the upper part of the left side of the septum. This is well known, and its importance cannot be neglected even if it does not make an entirely acceptable explanation.

What are the pathologic findings in regard to this problem? It is a common statement that Chagas' disease has a particular affinity for the conduction system. This is based on the disproportionate incidence of intraventricular and auriculoventricular conduction disturbances. We do not believe that this statement is entirely justified. Unfortunately, up to now, the conduction system has been histologically studied in only one case of acute[21] and four cases of chronic[20-23] chagasic myocarditis.* In those cases, practically every part of the conduction system which was studied was definitely involved by the inflammatory process, cellular infiltration predominating in the acute case, both cellular infiltration and fibrosis in the chronic cases. In no case was it stated that the lesions were more severe or abundant in the specific than in the ordinary muscle of the ventricles. Most probably, the specific tissue of the heart does no more than share its quota of the inflammatory process which diffusely involves almost the entire myocardium.

If we accept the fact that the conduction system may be more or less uniformly invaded by the inflammatory process, the most reasonable explanation for the higher incidence of right bundle branch block would be the greater

*In a naturally infected young dog, Mazza and Jorg[22] have reported the finding of parasites (Leishmania forms of *Schizotrypanum cruzi*) in the bundle of His.

delicacy or fragility of its conduction properties, compared with other sections of the specific system, especially of the left branch. As supported by many clinical and physiologic evidences, the right branch seems to be more functionally vulnerable than the left branch of the bundle of His. For instance, it is possible that in normal conditions the conduction of the impulse is slower in the right than in the left branch, the difference amounting to 0.01 to 0.02 sec.[39] (The same idea has been expressed by Wilson and associates[47] as indicating that even normally there is some degree of incomplete right bundle branch block.) Among further findings are the not uncommon observation of incomplete and complete right bundle branch block in normal individuals; the generally higher incidence of right as compared to left bundle branch block, in spite of the fact that in most cases of heart disease the left ventricle is the one primarily involved; and especially, the fact that aberrant intraventricular conduction in supraventricular arrhythmias affects far more often the right than the left branch system.[14,46]

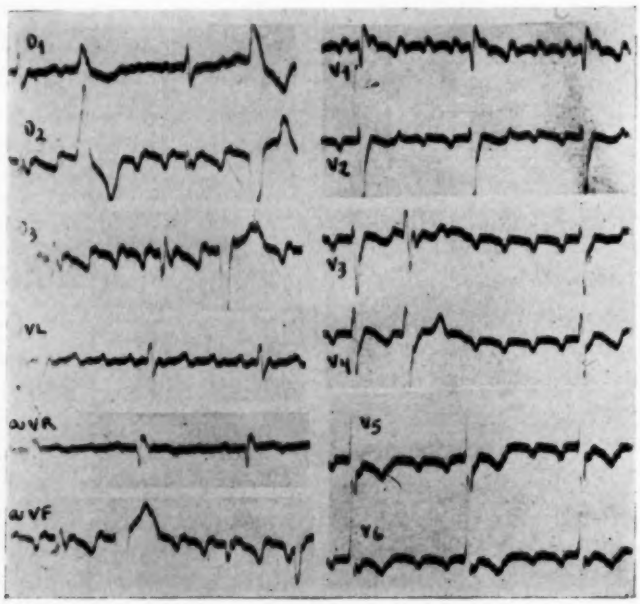


Fig. 11.—55-year-old man in severe heart failure. Atrial flutter with irregular A-V conduction (sometimes 4:1), incomplete right bundle branch block, and polymorphous ventricular extrasystoles. In spite of the tall flutter waves, primary T-wave changes can be seen in left precordial leads. Some months later the T waves became positive. A tracing taken during sinus rhythm showed auricular extrasystoles, nodal and ventricular escapes, numerous and polymorphous ventricular extrasystoles (one type of the ectopic beats corresponds to a parasystolic mechanism) and very bizarre alteration of the P waves. Positive xenodiagnosis.

In other words, we believe that the right branch is more prone to be affected than the left branch by any pathologic process which involves both in a similar extent (for physiologic more than for anatomic reasons). For instance, if the damage to the branches produced by the inflammatory process could be measured on a scale of grades from one to four, we could assume that when a

Grade 1 lesion exists in both branches, conduction will be interrupted in the right and not in the left branch and consequently the patient will have a right bundle branch block pattern. On the other side of the scale, a Grade 4 lesion in both branches would interrupt conduction in both the right and left branches and the patient will have a pattern of complete A-V block. Thus possibly left bundle branch block exists in many cases of chronic chagasic myocarditis, but as right bundle branch block is also present in these cases, it would not be possible to recognize it by the electrocardiogram, because bilateral complete bundle branch block is accompanied by complete A-V block. At least some of the chagasic cases of complete A-V block originate in this way. This is supported by the pertinent, though not conclusive fact that in three out of our five cases of chagasic complete A-V block, varying ventricular complexes were present—a finding which has been related to the existence of bilateral bundle branch block.[47]

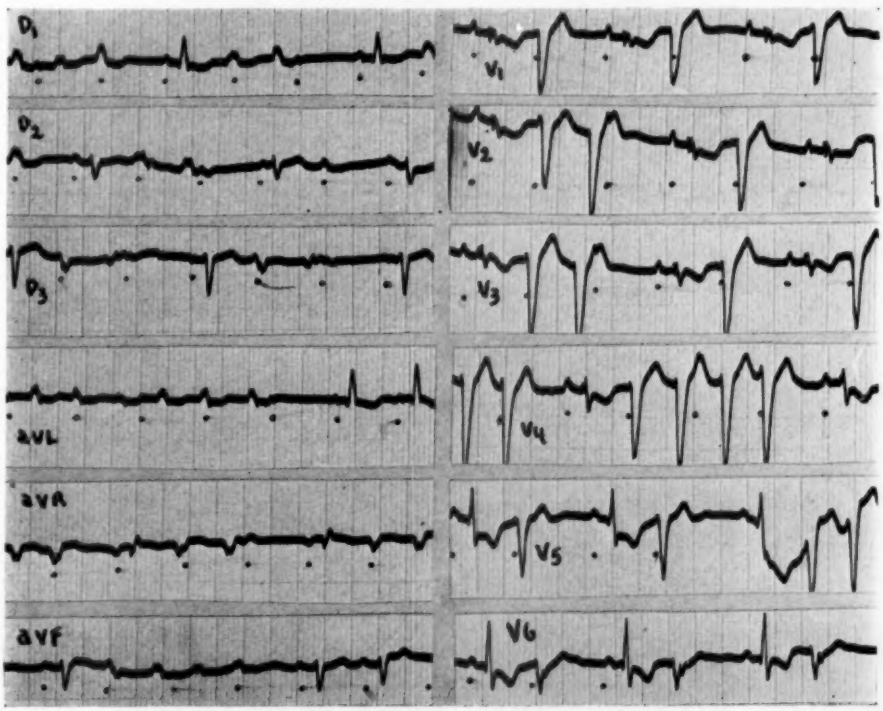


Fig. 12.—11-year-old boy in very severe heart failure and with considerable cardiac enlargement. He had repetitive episodes of paroxysmal rapid heart action which promoted a more rapid fatal outcome, three months after his admission. Incomplete right bundle branch block with pronounced left-axis deviation (as the latter would be very unusual for that age, this is a nice example of its relation to chronic chagasic myocarditis). Ventricular extrasystoles, isolated or in groups of 2, 3, or 4 ectopic beats. The dots indicate the place of the P waves. In other tracings, prolonged P-R interval, A-V dissociation with interference, auricular and ventricular extrasystoles, and episodes of auricular and ventricular tachycardia.

2. *T-wave Abnormalities.*—Abnormal T waves were present in 42.47 per cent (48 cases) of the 113 cases with abnormal electrocardiograms, thirty cases being accompanied by and eighteen cases not being accompanied by right bundle branch block. Owing to their high incidence, and also to the fact that they

may simulate coronary disease, T-wave abnormalities constitute one of the most important findings in chronic chagasic myocarditis. Some examples are illustrated in Figs. 4, 5, 7, 13, and 14.

We have already discussed the considerable diagnostic value of the T-wave abnormalities when observed in association with right bundle branch block. When this conduction disturbance is not present, they may constitute a more difficult diagnostic problem. In young people, especially women, with positive epidemiologic history and Guerreiro-Machado test, and without signs of any

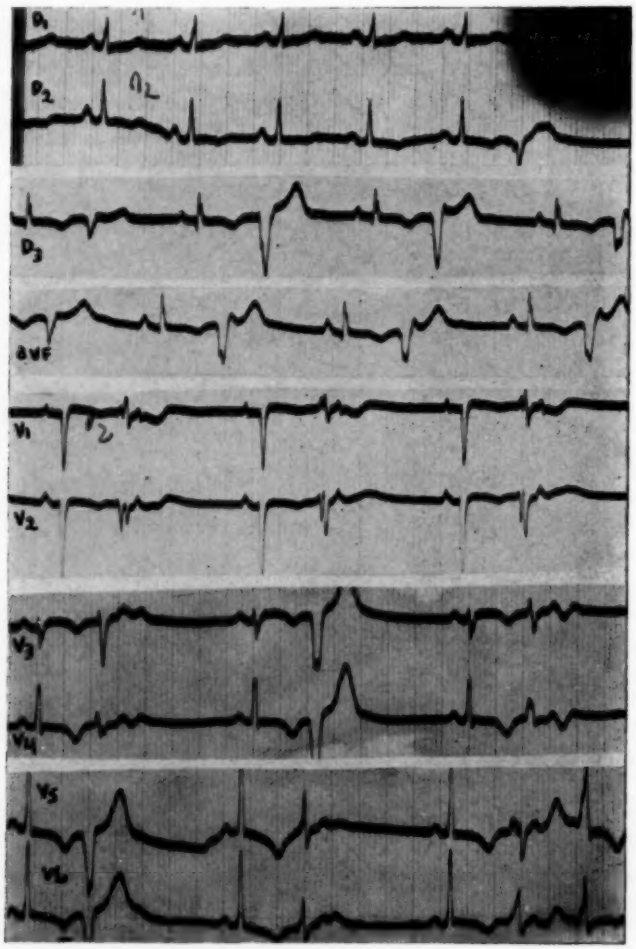


Fig. 13.—38-year-old woman, with moderate degree of heart failure. She died suddenly, when walking in the street, 10 months after her first examination. Abnormal T waves indicating extensive subepicardic myocardial involvement of the anterior and posterior aspects of the heart, as in the cases of Figs. 5 and 7. Very frequent ventricular extrasystoles, sometimes of the same morphology, as in V_1-V_2, sometimes of very different shapes, as in V_3-V_4 and V_5-V_6. The tall R waves in V_5 and V_6 suggest left ventricular enlargement.

other type of heart disease, they must be attributed to chronic chagasic myocarditis (Fig. 13), particularly if arrhythmias are also present. But in patients over 40 years of age, we have had occasionally very difficult problems, because it was not possible to rule out the presence of coronary heart disease, even when the patients did not have typical anginal pain or any other manifestation of

that disease. In cases like that, if the electrocardiogram only shows primary T-wave changes without any other abnormality, we believe that there is no adequate way of differentiating both conditions. The problem becomes even more difficult in cases in which both chronic chagasic myocarditis and coronary heart disease are present in the same patient, which does not seem to be exceptional. Chronic chagasic myocarditis can be observed in very old people, due to its slow evolution in some cases, and to the fact that the disease has been acquired late in life in others. At any rate, although it is true that such T-wave changes in old people could be accounted for by coronary arteriosclerosis in most of the cases, it will be wise to consider the possibility of chronic chagasic myocarditis as a second alternative in zones where Chagas' disease is endemic, particularly if other signs of coronary heart disease are not evident.

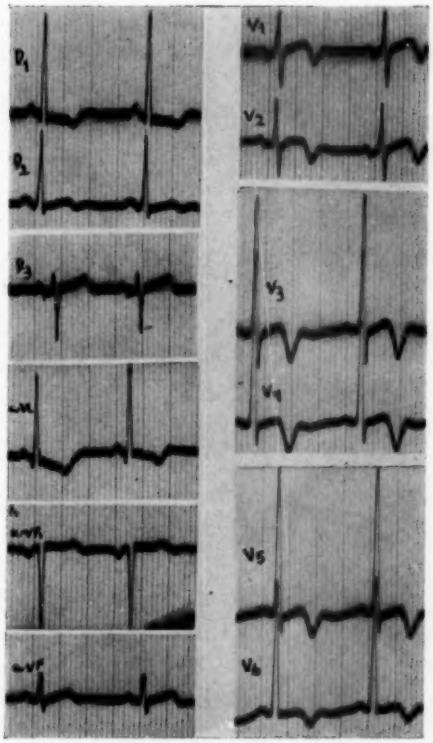
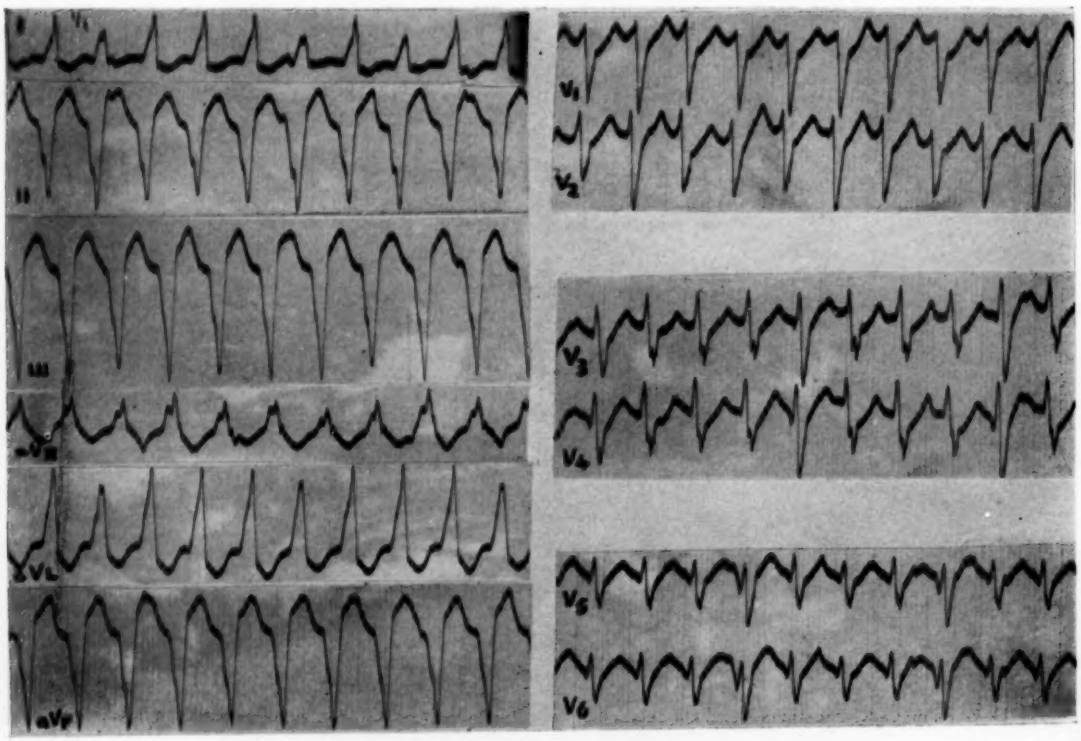


Fig. 14.—56-year-old man, asymptomatic. Four years previously he had the typical acute form of Chagas' disease, and apparently, an electrocardiogram was normal at that time (besides pronounced sinus tachycardia). Slightly elevated S-T segment and negative T waves in all the precordial leads. Typical signs of left ventricular enlargement.

In some of our cases the electrocardiogram displayed deeply inverted and pointed T waves, reproducing the typical configuration of the T waves in acute myocardial infarction. In addition, this type of negative T wave in Lead I was accompanied by reciprocal changes in Lead III (pointed and highly positive T waves) in a few cases (Fig. 4). In many cases, the T waves were negative in all the precordial leads, from V_1 to V_6; less frequently, only in aV_F and Leads II and III; in some cases in both, precordial leads and Leads aV_F, II, and III at the same time.

An important characteristic of these abnormal T waves was the absence of changes in tracings recorded at successive intervals, sometimes even after many years. That happened in most of our cases. However, in a few cases changes in the T waves were observed, only exceptionally in a very rapid sequence. Dias and co-workers[11] reported important and even rapid changes of the T waves in three out of twenty-two cases.

An elevated S-T segment, indicating "electrical injury" was observed in only one case (Fig. 14), showing neither progressive nor regressive changes. In general, there seems to be a difference between the electrical signs of "ischemia" and "injury" which can be observed in chronic chagasic myocarditis and in coronary heart disease. In the latter, the abnormal S-T and T waves



A.

Fig. 15.—52-year-old woman, with multiple episodes of paroxysmal ventricular tachycardia. Each of these episodes led the patient into a severe shocklike state. Only very high doses of Pronestyl or quinidine could control them but not prevent their further repetition. They were directly responsible for the death of the patient. The autopsy showed very severe and extensive myocardial lesions and revealed a predominantly subendocardial but almost transmural compact area of fibrosis in the posterior wall of the left ventricle. A ventricular aneurysm was present in the anterior wall of the left ventricle, close to the A-V groove (thickness of the wall at the level of the aneurysm: 2 millimeters). *A* shows one of the episodes of ventricular tachycardia. The P waves can be seen independently of the ventricular rhythm (the patient also had some episodes which could be identified as atrial flutter). *B* shows four tracings with sinus rhythm taken between the multiple episodes of paroxysmal tachycardia. Some of the S-T-T changes were due to quinidine and some could have been related to the crisis of tachycardia. The abnormal QR ventricular complexes in Leads aV_F, II, and III are well correlated with the area of fibrosis in the posterior wall. It is possible that, if precordial leads would have been taken at a higher level, abnormal QR and QS complexes would have appeared in front of the aneurysm. No coronary lesions were present at the autopsy.

are more likely to suffer progressive or regressive changes in a greater number of cases.

The T-wave changes of chronic chagasic myocarditis are well explained on account of the extensive myocardial lesions which the autopsy of these cases usually reveals. Moreover, it is not unusual for the inflammatory process to be more severe in the subepicardial than in the subendocardial region of the ventricles, accompanied or not by some degree of pericardial involvement.[43]

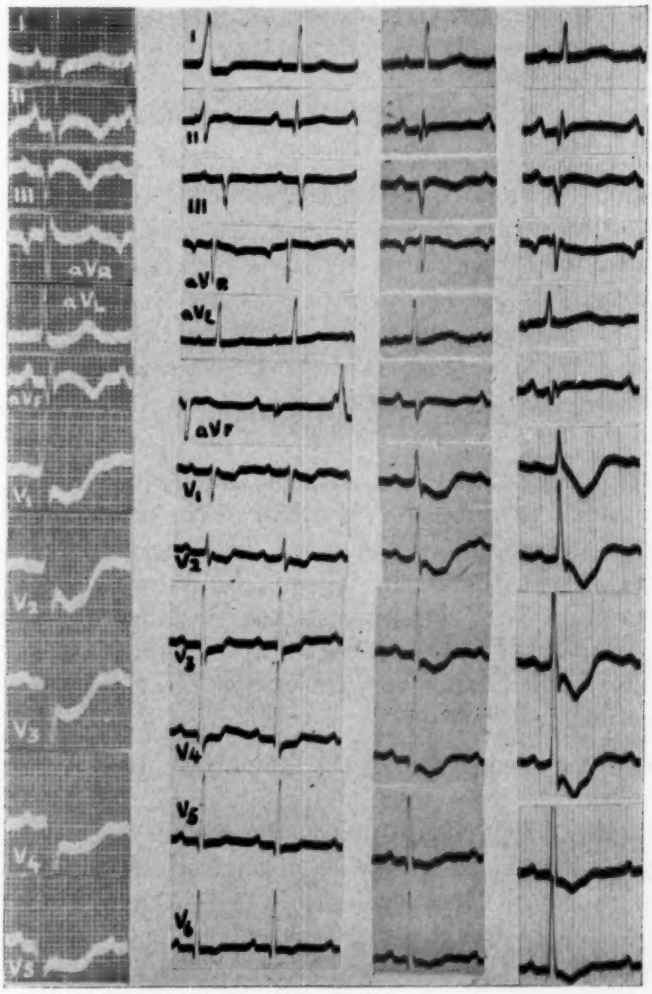


Fig. 15, *B*. *(For legend see opposite page.)*

3. *Ventricular Extrasystoles.*—Ventricular premature beats were present in 53.98 per cent (61 cases) of the group with abnormal electrocardiograms. In a great number of these cases, the ventricular ectopic beats were very abundant and persistent during long periods of time. In many patients who were followed during 2 to 4 years and submitted to monthly clinical and/or electrocardiographic examinations, the extrasystoles were present in every occasion. This makes us believe that at least in some cases, ventricular extrasystoles are almost constantly produced.

Very frequently the ventricular extrasystoles gave place to bigeminal rhythm, less frequently they occurred every third or fourth beat and short runs of 2, 3, or 4 consecutive beats of the same or different shape were often seen.

Some of the patients had been taking digitalis at the time when the extrasystoles were recorded, but in the majority, the ectopic beats were observed at a time when the drug was not given. They were more frequently present in patients with large hearts and in heart failure. In those cases, the administration of digitalis did not diminish the number of the extrasystoles, and it was hard to decide if they were increased because of the drug. But the same types of ventricular ectopic beats were also observed in many patients with normal-sized hearts and without any evidence of heart failure.

In an important group of cases, extrasystoles were not observed, even if they were looked for in many clinical and electrocardiographic examinations. There was a definite distinction concerning this point: the patients either had numerous extrasystoles every time they were examined or they never showed them at all. In a small group of cases the ectopic beats were only occasionally observed. In a few cases in which extrasystoles were not observed they appeared immediately after a short exercise test. The same test greatly increased their number in the cases in which they were already present at rest.

The most important characteristic of the ventricular extrasystoles was their polymorphism. In more than one-half of the cases, they showed at least two and not rarely three different shapes. In some cases, during more or less prolonged intervals of extrasystolic bigeminal rhythm, every ectopic beat had a different form (Fig. 8). This suggests the existence of many different foci, though the possibility of only one focus with conduction disturbances could not be completely ruled out. A parasystolic mechanism was demonstrated in five of the cases.

We have already emphasized the diagnostic importance of ventricular extrasystoles, when they are associated with right bundle branch block and abnormal T waves. They constitute, on the contrary, a very difficult problem when they are present in an otherwise normal electrocardiogram in a patient with the chronic form of Chagas' disease. On one hand, it is possible that in some cases they could be the initial electrocardiographic manifestation of chronic chagasic myocarditis.[9] On the other hand, ventricular ectopic beats are frequently devoid of any clinical significance and are a common occurrence in normal people. For that latter reason, we adopted the criterion advanced by Dias and co-workers[11] of not considering cases with ventricular extrasystoles and without other abnormalities as indicating chronic myocarditis, with only one exception. It was a 27-year-old woman, with a positive epidemiologic history and a positive Guerreiro-Machado test. Her only complaints were palpitations. The electrocardiogram showed as the only abnormality numerous ventricular extrasystoles from four different foci. No other abnormalities were present, neither clinically nor radiologically. Two other tracings showed only ventricular extrasystoles of unifocal origin. A few days after the last

tracing was recorded, the patient died with an atypical pattern of acute peripheral circulatory failure. The autopsy revealed very severe and extensive inflammatory myocardial lesions.

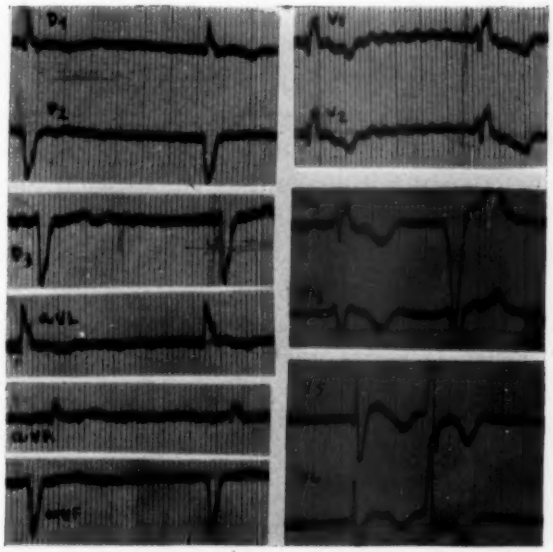


Fig. 16.—59-year-old man, with severe heart failure, followed during 27 months. Complete A-V block (ventricular rate, 44 beats per minute). Notice that the ventricular complexes have the right bundle branch block pattern, with pronounced left-axis deviation and almost absent S waves in Lead I, which are common in chronic chagasic myocarditis with sinus rhythm. Auricular fibrillation, primary T-wave changes, and ventricular extrasystoles. Other four tracings (during two years) were identical.

In only three of our cases, ventricular extrasystoles were observed unaccompanied by any other electrocardiographic abnormality. In these three cases our diagnosis was "chronic undetermined form of Chagas' disease without definite evidences of myocarditis." In the rest of the cases, important electrocardiographic alterations were also present, which facilitated the diagnosis. Ventricular extrasystoles were associated with right bundle branch block and primary T-wave changes in twenty cases; with right bundle branch block and no T-wave changes in ten (one of them with auricular fibrillation; another one with atrial flutter and a third one with a pattern of "left ventricular hypertrophy and strain"); with only primary T-wave changes in five; with various abnormalities (complete A-V block, auricular fibrillation, left ventricular hypertrophy, etc.) in twelve cases. In general, the ventricular extrasystoles were more frequent and polymorphous as the clinical condition and other electrocardiographic abnormalities were more severe.

Concerning their prognostic significance, ventricular premature beats were present in eight out of ten patients who died within the first two years of the observations, all of them suddenly. Sudden death has been repeatedly reported as frequent in chronic chagasic myocarditis, even in asymptomatic patients, with normal-sized hearts and without heart failure. It is justifiable to think that ventricular extrasystoles are directly related with this sudden death. In

fact, it is a well-known fact that ventricular ectopic beats may be, under certain conditions, the precursor of fatal ventricular tachycardia or fibrillation. Of course, this only happens in an extremely small percentage of the persons who have this arrhythmia. But actually, ventricular extrasystoles in Chagas' disease meet the conditions which make them a permanent threat of ventricular fibrillation, according to well-accepted clinical and physiologic standards, namely, their great frequency, persistence, and particularly their polymorphism. Even if it has never been shown that ventricular extrasystoles were responsible for sudden death in any particular case of chronic chagasic myocarditis, the preceding considerations are strongly consistent with that idea.

The previous statements do not mean that every patient with chronic chagasic myocarditis who has ventricular extrasystoles will always die in a short time. Two of our patients were followed during 15 and 18 years, respectively, and although ventricular extrasystoles were present on numerous occasions, they did not seem to influence the benign clinical evolution of those cases.

4. *A-V Block.*—Contrasting with all the other electrocardiographic abnormalities, A-V block was less frequent in ours than in the patients studied by Dias and associates.[11] Only five cases (4.4 per cent) of complete and eight cases (7.0 per cent) of incomplete A-V block were present in our 113 abnormal electrocardiograms. The corresponding incidences were, respectively, 10.0 and 38.8 per cent in Dias and co-workers' group. The difference is difficult to explain, for actually, as our group seemed to represent a more advanced stage of the disease, the contrary should have been expected.

Regarding incomplete A-V block, the difference could possibly be accounted for by dissimilarities in the human composition of the groups which are compared. Whereas young patients definitely predominated in the Brazilian group, in our group the average age of the patients was definitely higher. It is interesting to remark that in the same group of cases studied by Dias and co-workers,[11] incomplete A-V block was far more frequent than complete A-V block, and while the former was more commonly seen in young patients, the latter was almost always observed in the more advanced age group. It is possible that incomplete A-V block may occur in the more initial periods of the disease and later on is apt to regress. If the contrary would be the case, namely, if these abnormalities were progressive, complete A-V block would have been more frequent. It is also possible that patients with complete A-V block die earlier in the course of the disease and are therefore less likely to appear in a group of cardiac patients, but we would favor the former explanation. On the other hand, it is noteworthy that in the acute form of Chagas' disease, when intraventricular conduction disturbances are only rarely observed, first degree A-V block is one of the most important manifestations of heart involvement. It is then possible that the first degree A-V block that occurs in the acute form and in the early periods of the chronic form of Chagas' disease is simply a counterpart of the same type of abnormality of the P-R interval which accompanies many infectious diseases and particularly rheumatic fever, consequently having a different mechanism from the complete A-V block which is observed in severe

and advanced cases of chronic chagasic myocarditis. Ponde,[30] who found, too, a lesser incidence of incomplete A-V block in a series of hospital cases of chronic chagasic myocarditis, also considered that this form of conduction disturbance must be more frequent in initial than in advanced cases.

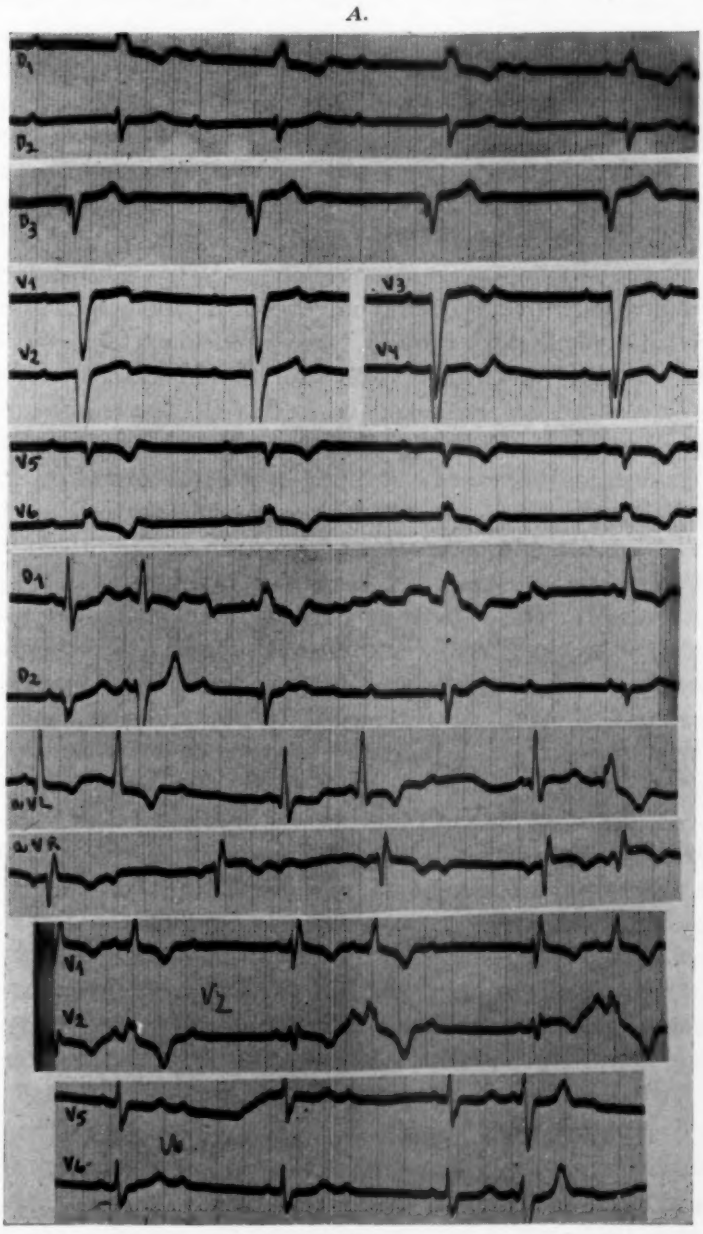


Fig. 17.—38-year-old woman. Only complaints: mild dyspnea on effort and palpitations. Her blood pressure oscillated between 170/90 and 200/100. *A* shows complete A-V block. The ventricular complexes are of the left bundle branch block type. *B*, taken about 50 days later, shows the same idioventricular beats and also conducted and possibly fusion beats and ventricular extrasystoles (Leads I, II, and aV_L). In aV_R and V_5-V_6, periods of 2:1 A-V block. The conducted beats show a right bundle branch block pattern, which was previously concealed by the complete A-V block. Numerous tracings during one and one-half year always showed complete A-V block.

Four of our five cases of complete A-V block were associated with severe heart failure and considerable heart enlargement. In the fifth case, the heart was only slightly enlarged and no heart failure was present. Auricular fibrillation was present in one case and atrial flutter which afterwards was transformed into fibrillation in another. Ventricular extrasystoles were very frequent in all five cases.

In the five cases the ventricular complex was 0.12 sec. or wider; in three of them, its form corresponded to the right bundle branch block pattern; in one, to the left bundle branch block pattern and in the last one, both types of patterns were alternately present, the right one most of the time. In three out of the five cases the true existence of right bundle branch block could be proved. In one of them, incomplete 2:1 A-V block with right bundle branch block was present prior to the development of complete A-V block. In the two other cases, ventricular captures were occasionally recorded, in which the ventricular complex showed a typical right bundle branch block pattern (in one of them, 10 years after complete A-V block was first demonstrated). This supports the contention advanced by Dias and co-workers,[11] that complete A-V block in chronic chagasic myocarditis many times conceals the existence of interrupted conduction in the right branch of the bundle of His. As already mentioned, the existence of changes of the ventricular pacemaker in three of the five cases suggests bilateral bundle branch block as the cause of the interruption of A-V conduction in at least these cases. Dias and co-workers[11] also emphasize the frequency of changes in the rate and shape of the ventricular pacemaker in cases of complete A-V block in chronic chagasic myocarditis. They attribute it to evolutive variations in the lesions produced by the *Schizotrypanum cruzi* in the myocardium. Barros,[3] when referring to four cases of chagasic complete A-V block, considers too the possibility of bilateral bundle branch block as the cause of them.

The clinical condition was far better in the eight cases with incomplete A-V block. Heart failure was only present in one of these cases. In two cases the heart was of normal size and only slightly enlarged in the others. Right bundle branch block was present in four cases and primary T-wave changes in one. In one of the cases with right bundle branch block and a slightly prolonged P-R interval (0.20 sec.), carotid sinus stimulation gave place to 2:1 A-V block and Wenckebach phenomenon, which disappeared after 1 mg. of atropine sulfate was injected intravenously. In the other seven cases, the incomplete A-V block consisted in a simple prolongation of the P-R interval to 0.20 sec. or more (first degree A-V block).

5. *Electrocardiographic Abnormalities Indicating Auricular Involvement.*—

(a) *P-wave abnormalities:* Widening, increased voltage, or notching of the P waves were observed in twenty-six cases (23 per cent). In none of these cases was the "mitral" or "pulmonale" type of P wave present.

In eight cases, some other etiologic factor which could have accounted for the abnormal P waves was also present. In two cases, no other electrocardiographic, radiologic, or clinical abnormalities were observed (the isolated P-wave abnormalities in these two cases were not considered sufficient to make a diag-

nosis of chronic chagasic myocarditis). Of the whole group, in sixteen cases the P-wave changes could strictly be related to the presence of chronic myocarditis. Six of the latter had severe heart failure and considerable heart enlargement (two of them with complete A-V block), that is to say, conditions in which, whatsoever the etiology, P-wave abnormalities are likely to be present. In the remaining ten cases, no heart failure was present and the heart was of normal size or only slightly enlarged. It then seems safe to assume that at least in those ten cases, the P-wave abnormalities indicated direct involvement of the auricular muscle by the parasite. This correlates well with the frequent finding of auricular muscle lesions in the autopsy of chronic cases of chagasic myocarditis.

(b) *Auricular extrasystoles* were present in fourteen cases (12.38 per cent). In all of them other important electrocardiographic abnormalities were also present. Severe heart failure and pronounced heart enlargement coexisted in seven of the cases. This arrhythmia does not seem to be an initial sign in the course of the disease, for it was never seen in the less severe or advanced cases.

Auricular extrasystoles did not seem to have a close relation with the presence of P-wave abnormalities, for in only six out of the fourteen cases were both observed together, whereas in twenty cases with abnormal P waves (out of twenty-six), no auricular extrasystoles were observed.

In seven cases, auricular and ventricular extrasystoles were present together in the same electrocardiogram.

(c) *Auricular fibrillation* was present in fourteen cases (12.38 per cent). As Dias and associates[11] have pointed out, auricular fibrillation has a serious prognosis and usually is accompanied by many other severe clinical manifestations of the disease. Severe heart failure and pronounced heart enlargement existed in ten of these cases. Four of them died in the first month and a fifth one two years after they were examined by us for the first time.

The following associated abnormalities were present in the fourteen cases of auricular fibrillation: right bundle branch block in seven; complete A-V block in two; primary T-wave changes in six; and ventricular extrasystoles in eleven cases. In three cases the auricular fibrillation was transient.

(d) *Auricular flutter* was observed in five cases (4.42 per cent), in three of them together with severe heart failure and pronounced heart enlargement. The other two patients, without heart failure and with only moderately enlarged hearts, had a chronic, well-tolerated auricular flutter.

6. *Miscellaneous Electrocardiographic Abnormalities Indicating Ventricular Involvement.*—

(a) *Left intraventricular conduction disturbances:* In twelve cases, notching and slurring of the R wave in left precordial leads were observed, in some of them with a delayed intrinsicoid deflection up to 0.06 to 0.08 sec. In five of these cases this was associated with right bundle branch block.

These were the kinds of electrocardiographic abnormalities which not infrequently develop in patients with pronounced and long-lasting left ventricular enlargement, for instance in hypertensive-coronary heart disease. In the twelve

cases of chronic chagasic myocarditis they were related to the presence of left ventricular enlargement, which was radiologically demonstrated in all of them. In some of the cases in which right bundle branch block was also present, the latter was of the Type IV of Bayley's classification whose association with left ventricular enlargement has already been discussed.

(b) *QRS abnormalities imitating myocardial infarction:* We have already seen how frequently T-wave abnormalities may simulate coronary heart disease in chronic chagasic myocarditis. Moreover, in some instances, even abnormal Q waves having all the accepted criteria for the diagnosis of myocardial infarction may also appear. The best illustration is furnished by the case of Fig. 15, which was the only one of this sort in our material in which an autopsy was performed. In a second case in which abnormal QR and QS ventricular complexes were present, a definite diagnosis between chronic chagasic myocarditis and myocardial infarction could not be made. It was a 30-year-old man with a typical positive epidemiologic history and positive Guerreiro-Machado test. His electrocardiogram showed what seemed to be an extensive anterolateral myocardial infarct, but he never had had precordial pain and his principal complaints were related to repeated crisis of paroxysmal ventricular tachycardia and multiple ventricular ectopic beats. Ten years later, when he was 40, his heart was only moderately enlarged and no heart failure was present. The electrocardiogram was unchanged. Ventricular extrasystoles were always frequent, but ventricular tachycardia did not recur in the last five years. This short history is presented to illustrate the great difficulties in making a definite clinical diagnosis in cases of this sort.

The absence of R waves in precordial leads has been previously reported in cases of chronic chagasic myocarditis,[3,11,18] and correlated with the presence of extensive areas of fibrosis and pronounced reduction in the thickness of the subjacent ventricular wall, particularly at the apex of the left ventricle. These extensive areas of fibrosis, which even may give place to typical ventricular aneurysms,[25] do not seem to be infrequent in the autopsy of cases of chronic chagasic myocarditis.[11,18] The histologic study usually can determine easily its inflammatory origin, but macroscopically and from an electrical point of view, they are the exact counterpart of the extensive areas of scarring produced by myocardial infarction.[25] It is then not surprising that abnormal QR and QS complexes can be observed in cases of chronic chagasic myocarditis.

(c) *Ventricular tachycardia* was recorded in seven cases. One of them was a typical case of chronic chagasic myocarditis, proved at autopsy. The paroxysmal episodes were almost continuously repeated, and only high doses of Pronestyl or quinidine could control them, but not prevent their further repetition. They were directly responsible for the death of the patient. A second case was an 11-year-old boy, with severe heart failure, in whom the paroxysmal episodes promoted a more rapid fatal termination. In a third case, coronary heart disease could not be ruled out as a coexisting etiologic factor. In two other cases, there were isolated and short runs of ventricular tachycardia in patients with considerable heart enlargement and heart failure. The last two

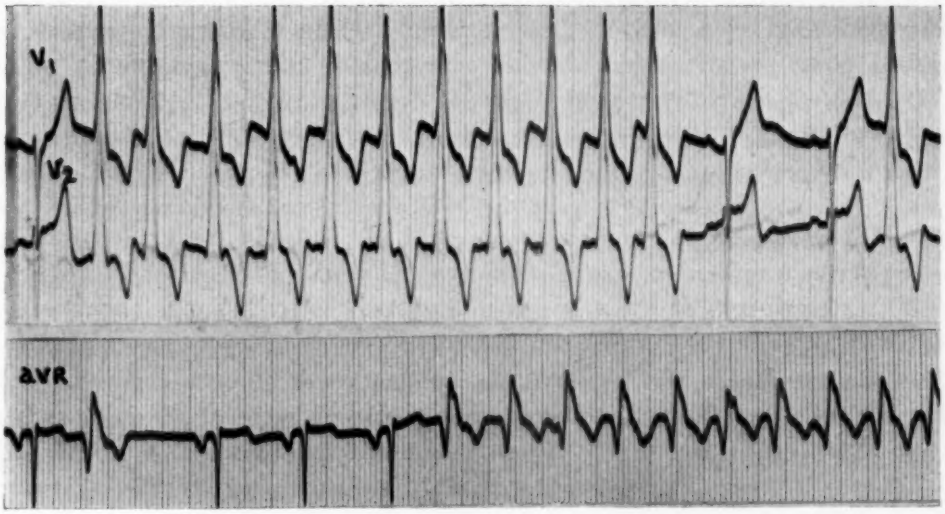


Fig. 18.—30-year-old man. Repetitive ventricular tachycardia. Fifteen electrocardiograms taken during the last 7 years were almost identical, always showing bouts of 2 to 25 successive ectopic beats alternating with isolated ventricular extrasystoles of the same configuration. This patient also had rheumatic heart disease, with mitral and aortic valvular lesions.

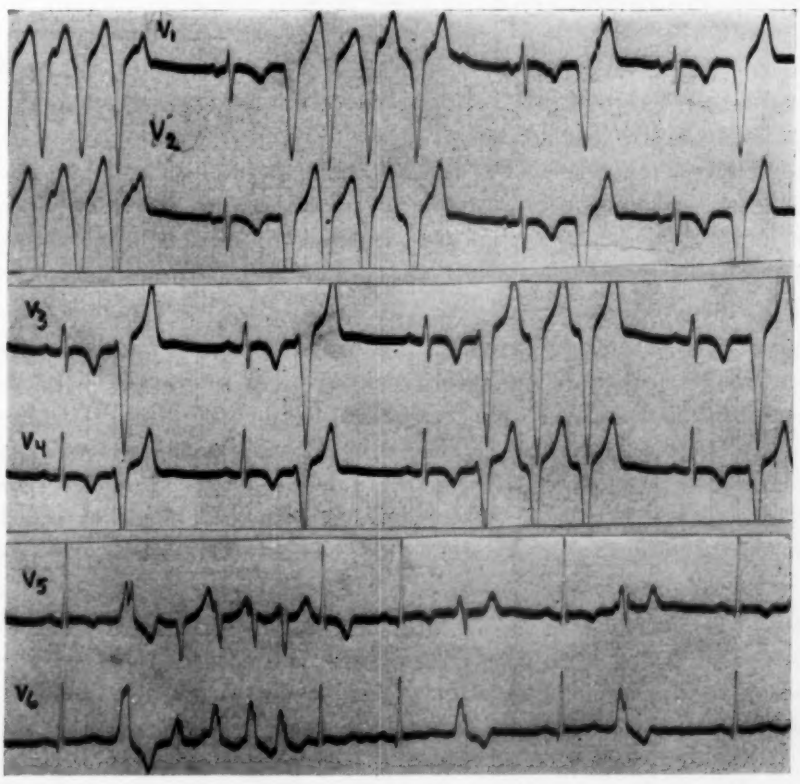


Fig. 19.—38-year-old man. Short bouts of ventricular tachycardia, alternating with single extrasystoles, sometimes giving place to bigeminal rhythm. Negative T waves in precordial leads. Only complaint: palpitations. Very slightly enlarged left ventricle. Notice postextrasystolic changes of the T waves (they were also negative in another tracing without extrasystoles).

cases were instances of repetitive and permanent ventricular tachycardia,[26] of the type initially described by Gallavardin,[13] well tolerated (in one case during 7 years, Fig. 18), with moderate heart enlargement and without heart failure.

7. *Arrhythmias.*—The most common type of cardiac arrhythmias have already been mentioned, as integrating the general electrocardiographic pattern, to which they contribute to give one of the most important and striking characteristics. In many cases (at least twelve), very complex arrhythmias were observed (ventricular and auricular parasystole, reciprocal rhythm, A-V dissociation with interference, nodal rhythm with ventricular extrasystoles, etc.). A detailed description of these is out of the scope of this paper and the most unusual will be published in separate papers.

Sinus arrhythmia and bradycardia, sinus depression after auricular and ventricular ectopica beats, and ventricular escapes were strikingly frequent.

8. *Left Ventricular Enlargement.*—There was a fundamental difference concerning this subject between our patients and those studied by Dias and co-workers.[11] While the latter did not report this finding in any of their cases, the incidence was as much as 22.12 per cent (twenty-five cases) in our group. Probably the most important reason for such a difference lies in the diagnostic criteria utilized, for we were able to recognize unquestionable cases in some of the electrocardiograms reproduced in their paper. It is important to bear in mind that from the time their paper was published, some new electrocardiographic signs for the diagnosis of left ventricular hypertrophy have been put forward and subjected to better clinical correlation[36] so as to make the diagnosis easier even in the less advanced forms. Even so, it is curious that in no cases of their large material a "typical pattern of left ventricular strain" was present while this pattern was not unusual in our group of cases (Figs. 10 and 14). But further publications by the same group of authors[18] showed cases in which the typical patterns of "left ventricular hypertrophy and strain" were present rather commonly.

We have already discussed the frequency with which chagasic right bundle branch block is accompanied by pronounced left-axis deviation. In cases without right bundle branch block this was also a frequent finding. Barros[3] relates the pronounced left-axis deviation, which he also observed as frequent in cases of chronic chagasic myocarditis, to left ventricular hypertrophy and dilatation. He also refers to seven cases in which the intrinsicoid deflection was inscribed at 0.06 sec. or later in left precordial leads. This has also been previously discussed in this paper.

We were careful to make sure that chagasic myocarditis per se is able to produce an electrocardiographic pattern of "left ventricular hypertrophy," by eliminating ten cases in which some other etiologic factors could have been responsible for the abnormal pattern. Thus we were left with at least fifteen cases (13.27 per cent) in which no other condition but the chronic chagasic myocarditis could have produced the pattern of "left ventricular hypertrophy."

When right bundle branch block was not present, the diagnosis of left ventricular hypertrophy was rather easy, and it was generally based on the usual

criteria (typical S-T-T changes, high voltage of the QRS, delayed intrinsicoid deflection, etc.). When right bundle branch block was present, the problem was a more difficult one. This conduction disturbance has a trend to conceal some or many of the signs of left ventricular hypertrophy. Under this condition, a valuable sign was the left-axis deviation, as already discussed.

In all the cases in which the electrocardiographic diagnosis of left ventricular enlargement was made, confirmatory evidence was furnished by radiologic examination and in some of them also clinical signs of left ventricular hypertrophy were present. On the other hand, in many cases in which fluoroscopy demonstrated left ventricular enlargement, sometimes even well pronounced, the electrocardiogram was completely noncontributory. That is contrary to what happens in cases of left ventricular enlargement of other etiologies; for generally, the electrocardiogram is more sensitive than fluoroscopy in detecting enlargement of the left ventricle, especially in initial forms. One possible reason for this is the great incidence of right bundle branch block, which may, as we already mentioned, conceal some of the electrocardiographic signs.

This relatively high incidence of left ventricular enlargement in cases of chronic myocarditis is particularly interesting, for it is generally accepted that "myocarditis" does not produce ventricular hypertrophy. Probably the reason why ventricular hypertrophy has not been reported in other types of myocarditis is that in practically all of them the clinical evolution is acute or subacute, never as prolonged as in the case in chronic chagasic myocarditis. In fact, probably Chagas' disease is the only one which affords the possibility of studying large series of cases of a chronic inflammatory process of the myocardium, without other parts of the heart being affected. What textbooks describe as clinical, radiologic, and electrocardiographic manifestations of "myocarditis" has very little to do with chronic chagasic myocarditis. The prolonged evolution and the intensity and distribution of the lesions in the heart give place to different and characteristic findings in the latter case.

We cannot say in how many cases of chronic chagasic myocarditis studied at autopsy the left ventricle is hypertrophic, but we believe that in at least a good number dilatation of the left ventricle predominates over thickening of the wall, as was the case in all our five autopsied cases in which the thickening was slight or absent. It is interesting that in one of these cases a typical pattern of the so-called "left ventricular hypertrophy and strain" was present. For that reason, we prefer the term "left ventricular enlargement" when referring to that electrocardiographic pattern. On the other hand, clear instances of thickening of the left ventricular wall were reported by Laranja and co-workers.[18] The most convincing case was the one published by Mazza and associates[23] in 1938. A 16-year-old girl had a typical chronic chagasic myocarditis without any other complicating disease. At the autopsy, the maximal thickness of the left ventricular wall was 25 millimeters.

In none of our cases were signs of right ventricular hypertrophy present. This fact supports our impression that chronic chagasic myocarditis is initially or dominantly a type of left-heart disease.

IMPORTANCE AND DIAGNOSTIC VALUE OF THE ELECTROCARDIOGRAM IN CHRONIC CHAGASIC MYOCARDITIS

We have stressed in a previously reported paper[1] that the electrocardiogram becomes abnormal before the heart enlarges and before clinical symptoms and signs are noticeable, in practically every case of chronic chagasic myocarditis. In advanced or severe cases, this is unimportant from a diagnostic point of view, for then the existence of myocardial involvement is self-evident. On the contrary, this is important in the less advanced or initial stages of the myocardial inflammatory process. In fact, under these conditions, when the existence of a chronic form of Chagas' disease has been demonstrated (by positive epidemiologic history and laboratory tests), the electrocardiogram turns out to be the only available clinical procedure capable of demonstrating whether or not myocardial lesions are already present. Moreover, many times the electrocardiogram may show multiple abnormalities when no other clinical or radiologic manifestations have yet appeared. It is quite clear that if the clinician should wait until heart enlargement, signs of heart failure, etc., appear before making the diagnosis, he will certainly miss a great many initial cases. This emphasizes the fundamental value which the electrocardiogram has in the diagnosis of chronic chagasic myocarditis.

The diagnostic value of each electrocardiographic abnormality has already been discussed, and particular emphasis laid on the association of right bundle branch block with primary T-wave changes and multiple and polymorphous ventricular extrasystoles, with or without left-axis deviation of the QRS. Let us insist on the difficulties created when some of these abnormalities are observed as an isolated finding. The most careful judgment is required before assuming that an isolated instance of right bundle branch block, or T-wave changes, or A-V block, etc., indicate that the patient actually has chagasic myocarditis. On the other hand, the greatest caution will also be necessary before ruling out this diagnosis. The dogmatic adoption of either one or the other of these two possible positions will inevitably give place to many erroneous diagnoses. Careful evaluation of all the coexisting clinical circumstances and sometimes only the close follow-up of the patient will lead to the most satisfactory clinical decision. In some cases, only a presumptive diagnosis is advisable or the only possibility.

When the electrocardiogram is normal, the best diagnosis is "chronic form of Chagas' disease" with the assumption that myocarditis is not present. Under these conditions, the expression "potential heart disease," as established by the American Heart Association is also adequate. We only know of one proved reported case of chronic chagasic myocarditis in which the electrocardiogram was normal.[3] A second case was presented in this paper (though multiple and polymorphous ventricular extrasystoles were observed on one occasion). These are only rare exceptions to the general rule that a normal electrocardiogram practically rules out the possibility of chronic chagasic myocarditis.

SUMMARY

1. Electrocardiographic abnormalities were present in 113 (86.92 per cent) out of 130 cases of the chronic form of Chagas' disease studied in the "Pabellón de Cardiología Luis H. Inchauspe", Policlínico Ramos Mejía, Buenos Aires.

2. In the abnormal group of electrocardiograms, the highest incidence was shown by the following findings: right bundle branch block, 55.7 per cent; ventricular extrasystoles, 53.9 per cent; primary T-wave changes, 42.4 per cent; P-wave abnormalities, 23.0 per cent; left ventricular enlargement, 22.1 per cent.

3. A comparative study of sixty-three cases of chagasic with sixty-five cases of nonchagasic right bundle branch block showed that the former is more frequently accompanied by other electrocardiographic abnormalities. The association of right bundle branch block with primary T-wave changes and multiple and polymorphous ventricular extrasystoles was found very valuable for the diagnosis of chronic chagasic myocarditis. In more than 50 per cent of the chagasic cases of right bundle branch block, there was pronounced left-axis deviation of the QRS. Chagas' disease was found to be an important cause for right bundle branch block in Buenos Aires, and it is possible that it is the most important of all in endemic areas in the country. Right bundle branch block in a patient with the chronic form of Chagas' disease would indicate that chronic myocarditis is actually present in at least 85 per cent of the cases.

4. Contrasting with right bundle branch block, left bundle branch block is seldom seen in chronic chagasic myocarditis. The possible reasons for this difference are discussed. An explanation is advanced which depends on the two following facts: (a) the degree of inflammatory involvement seems to be usually about the same in both branches of the bundle of His; (b) the right branch is anatomically and especially functionally more vulnerable than the left branch. If the bilateral lesions are not important, right bundle branch block would be produced; if they are severe, complete A-V block would occur. Consequently, an electrocardiographic pattern of left bundle branch block could only appear if the lesions are much more severe in the left than in the right branch.

5. The diagnostic value of each isolated electrocardiographic abnormality is discussed, and the difficulties for a definite diagnosis in some cases are pointed out.

6. Chronic chagasic myocarditis may give place to abnormal QR or QS ventricular complexes, of the same type as observed in myocardial infarction. However, this is a relatively infrequent event. The anatomic reasons for that are explained. More frequent is the presence of abnormal T waves of the "coronary" type, related to the existence of intense subepicardial lesions.

7. Pure cases of chronic chagasic myocarditis may produce a typical pattern of the so-called "left ventricular hypertrophy and strain." Both dilatation and thickening of the left ventricular wall can cause this electrocardiographic pattern.

8. The electrocardiogram is the best method for the diagnosis of initial forms of chronic chagasic myocarditis.

SUMMARIO IN INTERLINGUA

In un serie de 130 patientes con le forma chronic de morbo de Chagas, le electrocardiogramma esseva anormal in 113 casos (86,92 pro cento). Le plus frequente constationes esseva bloco del branca dextere (55,7 pro cento), extrasystoles ventricular (53,9 pro cento), alterationes primari del unda T (42,4 pro cento), anormalitates del unda P (23,0 pro cento), e allargamento sinistroventricular (22,1 pro cento).

Un tracto de grande valor in le diagnose de chronic myocarditis chagasic esseva le association de bloco del branca dextere con alterationes primari del unda T, e multiple e polymorphe extrasystoles ventricular.

In contrasto con le frequentissime constatation de bloco del branca dextere, bloco del branca sinistre esseva trovate solmente in casos exceptional. Le possibile rationes pro iste differentia es discutite.

Anormalitates del complexos ventricular QR e QS non esseva absente del serie. Il esseva constatate que casos pur de chronic myocarditis chagasic pote producer le configuration electrocardiographic del si-appellate "hypertrophia e effortio sinistroventricular." Le causa de iste configuration pote esser dilatation o spissification del pariete sinistroventricular.

We wish to express our appreciation to Dr. E. Lepeschkin for his kind help in preparing the English version of this paper.

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THE CORRECTED Q-T DURATION IN ACUTE AND CONVALESCENT RHEUMATIC FEVER*

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IN RECENT years the clinical significance of the Q-T interval of the electrocardiogram has become more fully understood. Use of this measurement has extended to electrolyte problems, heart failure, drug effect, tests of exertion, and carditis.

The problem of assessing low-grade activity of rheumatic fever is always a vexing one for the clinician. Extensive experience has proved that no single test is infallible, and often after a whole spectrum of clinical and laboratory observations the issue remains in doubt. Any test which would add to the accuracy of establishing rheumatic activity would be widely welcomed.

Several observers have reported that the Q-T interval of the electrocardiogram is prolonged in an impressive number of cases of acute carditis. Taran and Szilagyi[1-3] have been outspoken advocates of the use of this measurement. They have reported a direct relationship in their cases between the Q-T measurement and rheumatic carditis, with the implication that there may be a linear correlation between this value and the degree of severity of the carditis. Pokress and Goldberger[4] studying children up to the age of 20, noted Q-T prolongation in 28 per cent of the cases of active carditis, although these investigators ob-observed that 30 per cent of the active cases had no Q-T prolongation during the period of observation. Bellet and Finkelstein,[5] studying the significance of increased Q-T duration, found myocardial abnormality or disease as a cause in 20 of 168 cases. Sixteen were considered to result from myocarditis and 13 were of rheumatic etiology. Gittleman and associates[6] reported the Q-T interval of value in the diagnosis of carditis, although the results in cases of rheumatic etiology were less impressive than in the nonrheumatic group. In 62.2 to 81.0 per cent of nonrheumatic myocarditis depending on the formula used, the Q-T was prolonged. The values for the rheumatic group were 21.4 to 35.7 per cent. Joos and associates,[7] using the Bazett formula, found a mean K (the constant) of 0.405 in their control group of children. Eighty-four per cent of the cases of active rheumatic fever had a K value exceeding 0.424, and a further increment of 12 per cent had K values between 0.415 to 0.424. In quiescent rheumatic fever the value of 0.424 was exceeded by 12 per cent, and 19 per cent fell into the group between 0.415 to 0.424.

Received for publication Feb. 21, 1955.

*The opinions and assertions are the private ones of the author and are not to be construed as official or reflecting the view of the Navy Department or naval service at large.

Solomon and Zimmerman[8] found K to equal 0.422 or less in 92 per cent of their control population in the pediatric age group. In active rheumatic fever 84 per cent of the cases yielded K values exceeding 0.422 and 100 per cent were above 0.405. In only 8 per cent of their control series did K exceed 0.422. Forty-four per cent of this control group had K levels above 0.405. It was their impression that Q-T changes in active carditis were more frequently observed than the sum of other reported electrocardiographic abnormalities.

Craige, Alimurung, and co-workers,[9,10] studying a large group of control children and rheumatic fever patients at the House of the Good Samaritan, Boston, were unable to confirm the results of Taran and others. By their technique no consistent pattern was observed. They observed that cases with fatal pancarditis had a Q-T duration falling within two standard deviations of Bazett's curve with a mean K of 0.404. Epstein and Gardam[11] working with 55 children, considered K of 0.410 or greater as abnormal. Their study showed K to exceed this level in 38 per cent of the cases during rheumatic activity and in 27 per cent while inactive. Seventy-six per cent of cases showed a significant prolongation where there was either pancarditis or failure. Their studies indicated that the Q-T was not prolonged in all cases of carditis and their conclusion was that Q-T prolongation in rheumatic fever occurred no more frequently than the incidence of accepted abnormal electrocardiographic evidence of active carditis. Finkel and Baldwin[12] observed that a significant number of children showed increased Q-T duration during the acute illness, but during the inactive phase a number retained prolonged Q-T values. They did not think that a continued Q-T prolongation was definite evidence of rheumatic activity.

TECHNICAL PROBLEMS

Technical problems have contributed to some of the divergent results obtained in studies of the Q-T interval in rheumatic fever, as well as its analysis in other clinical entities. In general these include: (1) selection of the proper formula from the large number presently in use; (2) agreement on the number of cycles necessary to obtain representative values; (3) problems associated with the actual measurement; (4) selection of the proper lead or leads to utilize in measurement; (5) age and sex difference in Q-T value; (6) dysrhythmias and conduction defects.

Formulas.—Because the Q-T interval lessens with increasing heart rate the relationship to the cycle length has been expressed by formulas utilizing many mathematical techniques. Excellent reviews are to be found in papers by Krasnoff,[13] Gittleman and associates,[6] and in the work of Lepeschkin.[14] In most common use are the square root formula (Bazett) $QT=K \cdot \sqrt{\text{cycle}}$ and the logarithmic formula (Ashman) $QT=K \cdot \log [10(R\text{-}R + 0.07)]$. The upper limit of normal for K in the Bazett formula by the Shipley and Hallaran[15] modification is 0.443 (male), and 0.456 (female).

Number of Cycles.—There has been no agreement on the number of cycles to measure in order to obtain an accurate figure indicative of the average cycle

length and Q-T value. Schlamowitz[16] recommended a single "representative" cycle. Lepeschkin[14] suggests an average of three continuous beats with all beats of a respiratory cycle being averaged in cases where a respiratory arrhythmia exists. Alimurung and associates[10] averaged three consecutive cycles and Craige and associates[9] used eight to twelve cycles in the rheumatic group. Elek and associates[17] recommend the use of five consecutive cycles, while Gittleman and associates[6] and Porkress and Goldberger[4] used ten cycles with a general average. Shipley and Hallaran[15] averaged eight to ten cycles. DeLalla and Brown[18] have suggested measuring the longest and shortest values in one complete respiratory cycle. Ashman[19] used an average cycle length in sinus arrhythmia and the "average value of several cycles" in other cases. Adams[20] measured and averaged fifteen consecutive cycles in his initial group but decided on statistical grounds that five cycles were adequate. Krasnoff[13] used five cycles in each of four leads, and Taran[21] advocated the use of twelve cycles in six leads with the Q-T_c (K) being derived from an average of these measurements. Taran and Szilagyi[22] also recommended an average of six seconds of continuous electrocardiographic recording in three standard and three chest leads.

Problems Associated With the Actual Measurement.—Lepeschkin and Surawicz[23] and Taran and Szilagyi[22] have reviewed these problems. The former authors have summarized them by an individual analysis of the isoelectric beginning of the T wave, isoelectric end of the T, notched T mistaken for a U wave, U wave mistaken for T wave, superposition of the U wave on the T wave, and superposition of auricular complexes on the T wave. Various mechanical devices to assist in measurement have been described. A standard hand magnifying glass is readily available and has proved to be reasonably accurate.

Selection of the Proper Lead.—Each lead individually and many lead combinations have been advanced by various authors. The majority of the early studies upon which most formulas were based utilized standard Lead II.

Age and Sex Difference.—All formulas reflect the relatively longer Q-T in the female. Very young children also have an increased Q-T duration.

Dysrhythmias and Conduction Defects.—The problem of the average measurement and of hysteresis of the Q-T becomes important in these situations. Lepeschkin[14] has reviewed the problems associated with conduction defects, and in auricular fibrillation recommends measurement of at least ten consecutive cycles.

MATERIAL AND METHODS

Healthy sailors received a cardiac history, physical examination, and blood pressure recording. Those with a history of rheumatic fever or abnormal cardiac findings were excluded. Two hundred normal men in the military age group were accepted as a control population and 12-lead electrocardiograms obtained. The test population included 110 cases with unequivocal acute rheumatic fever from the wards of the U.S. Naval Hospitals, Great Lakes, Ill., (1952-53) and

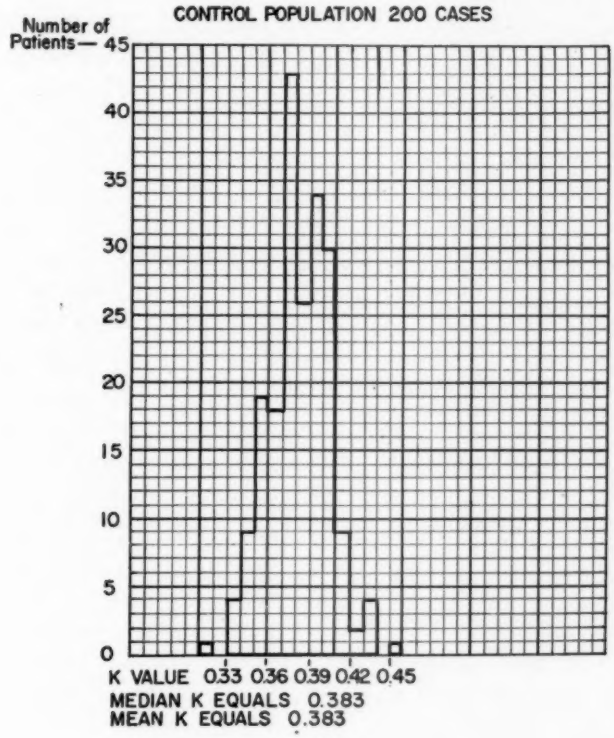
CONTROL POPULATION 200 CASES
Number of Patients— 45
40
35
30
25
20
15
10
5
0
K VALUE 0.33 0.36 0.39 0.42 0.45
MEDIAN K EQUALS 0.383
MEAN K EQUALS 0.383

Fig. 1.

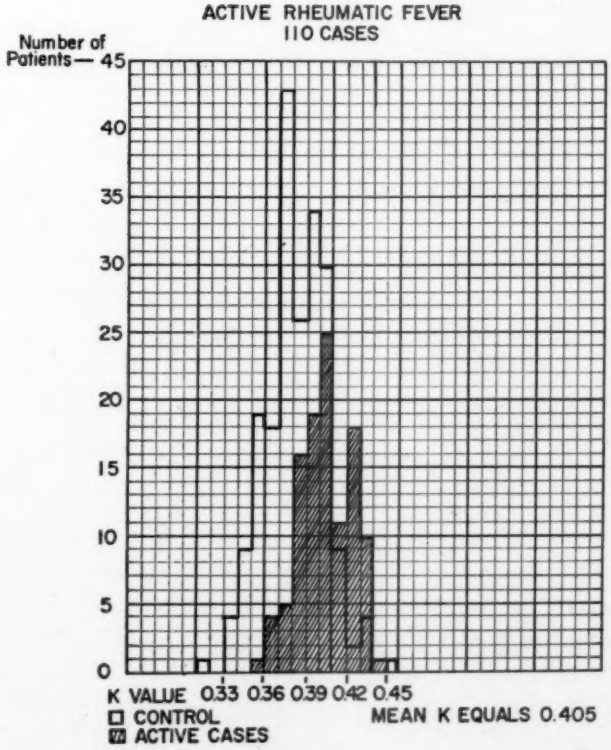
ACTIVE RHEUMATIC FEVER
110 CASES
Number of Patients— 45
40
35
30
25
20
15
10
5
0
K VALUE 0.33 0.36 0.39 0.42 0.45
CONTROL
ACTIVE CASES
MEAN K EQUALS 0.405

Fig. 2.

San Diego, Calif. (1954). The criteria set forth by Jones[25] were adhered to in the selection of cases. Tracings were obtained at admission during the acute phase of illness, and at least one tracing was analyzed during the late convalescent period when all measurable signs of rheumatic activity had subsided.

Tracings were taken with the same five machines (four Sanborn Viso-Cardiettes, one Cambridge Simpli-Trol) which had been checked for proper timing by a factory representative. All measurements were made by the author and Lead II was utilized. In the event comparative measurements indicated that either the initial portion of the QRS or the final portion of the T wave were isoelectric Lead I was substituted. No cases were accepted where the grade of A-V block caused superposition of a P on the preceding T, where premature contractions were frequent, or where A-V nodal rhythm, Wenckebach intervals, or bundle branch block appeared. In the test group no case was measured where T_2 was inverted. Cases with pericarditis were excluded.

A minimum of five consecutive cycles were measured and averaged. Where a significant respiratory arrhythmia appeared, all beats in a complete respiratory cycle were averaged.

Control data were analyzed and compared to the standard formulas in common use. The derived curve compared closely with results obtained using the Bazett formula with a mean K of 0.383 (Fig. 1). The Schlamowitz formula which had been derived from a similar control population was found to yield values too low for accurate comparison.

RESULTS

Review of the figures reveals that the mean and median K in the control population were both 0.383. Ninety-two per cent of the controls had a K of 0.410 or below, and 96.5 per cent were 0.420 or below. In active rheumatic fever the mean K was 0.405, and 26.3 per cent of the cases exceeded 0.420 (Fig. 2). Taking a K value of 0.420 as the upper limit of normal it is seen that over 25 per cent of the cases of acute rheumatic fever compared to 3.5 per cent of the control population exceeded this level. After the acute phase of rheumatic fever had subsided and all clinical evidence of activity abated the electrocardiograms were repeated and the mean K was 0.400 (Fig. 3). Sixteen and one-third per cent of this group had K determinations in excess of 0.420. In 68 cases the K fell as the rheumatic process subsided; however in 42 patients the K rose as the patient improved.

DISCUSSION

It is obvious from the data that K becomes significantly prolonged in more than one-fourth of the patients in this age group who develop acute rheumatic fever. It is similarly apparent that no definite conclusion can be drawn about rheumatic activity from a given K determination. There is too much overlap as demonstrated by Fig. 4. Earlier reports have been widely divergent about the use of this value as an indicator of rheumatic activity. By this technique and in this age group, the determination has no significance. Of greater interest is speculation on the reasons for K prolongation during rheumatic inactivity.

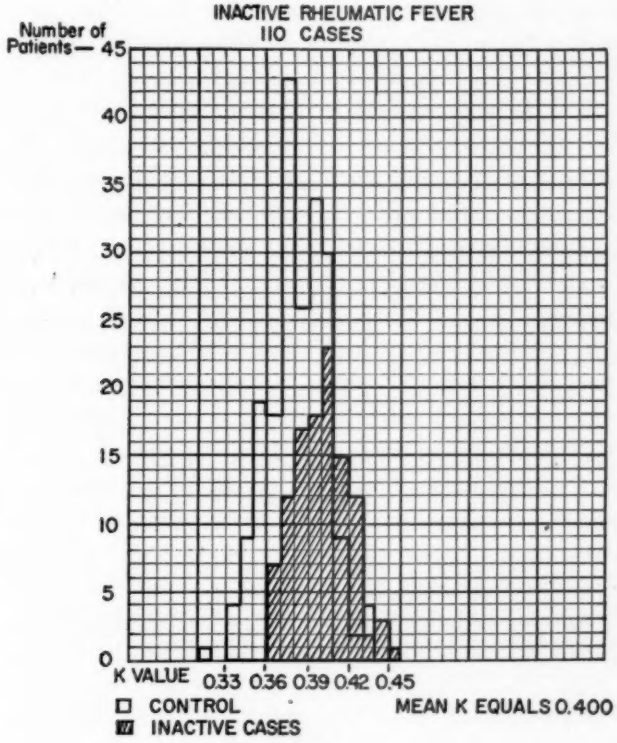
INACTIVE RHEUMATIC FEVER
110 CASES
Number of Patients — 45
40
35
30
25
20
15
10
5
0
K VALUE 0.33 0.36 0.39 0.42 0.45
CONTROL
INACTIVE CASES
MEAN K EQUALS 0.400

Fig. 3.

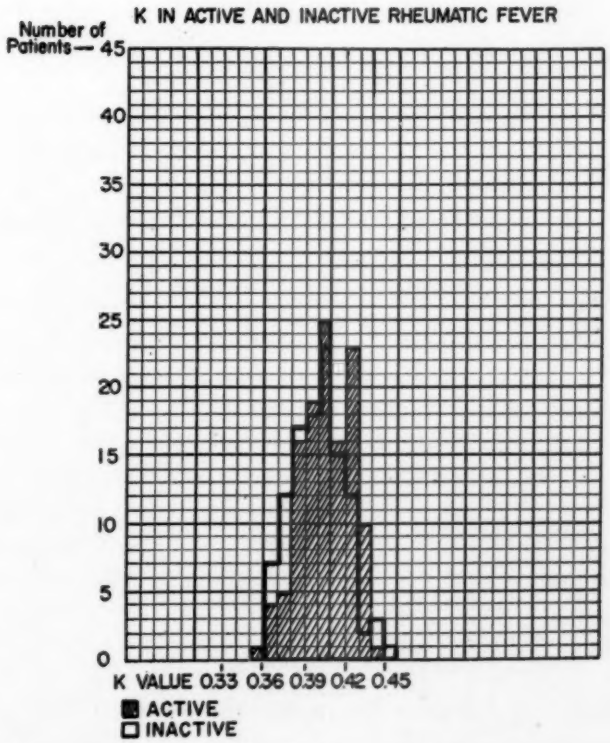
K IN ACTIVE AND INACTIVE RHEUMATIC FEVER
Number of Patients — 45
40
35
30
25
20
15
10
5
0
K VALUE 0.33 0.36 0.39 0.42 0.45
ACTIVE
INACTIVE

Fig. 4.

Since all measurements were made by the same technique and by the author, this difference seems quite definite. A similar finding has been reported in other series testing the Q-T interval in rheumatic inactivity.[11,12] It has been suggested that the Q-T is increased in debilitated patients, and it is possible that prolonged bed rest might lead to physiologic changes altering this value. Of greater probability is the fact that an appreciable number of patients developed cardiac enlargement during the illness. Again the literature is divided on this point. Elek and associates[17] felt that their studies established the absence of Q-T prolongation in left ventricular hypertrophy in cases with classical and advanced electrocardiographic changes. Their graph shows very minimal Q-T prolongation. Phang and White[26] used the Bazett formula and found that in six males and five females with cardiac enlargement and no congestive failure, a Q-T increase was observed. Bellet and Finkelstein[5] quote Fredricia who found the Q-T increased in cardiac enlargement and attributed it to cardiac weakness. Epstein and Gardam[11] noted that in 50 per cent of their group with cardiac enlargement and apparent health there was a Q-T prolongation, and Solomon and Zimmerman[8] relate that their cases with K above 0.422 and inactive rheumatic fever had valvular disease. It seems possible that cardiac enlargement may be the principal cause for the K prolongation as a late effect in rheumatic fever.

TABLE I

CASE	Q-T_c (TARAN TECHNIQUE)	K (5 CYCLES)
1. Active	0.423	0.428
Inactive	0.409	0.404
2. Active	0.397	0.390
Inactive	0.384	0.379
3. Active	0.436	0.429
Inactive	0.429	0.418
4. Active	0.419	0.420
Inactive	0.408	0.406
5. Active	0.396	0.390
Inactive	0.373	0.378
6. Active	0.379	0.386
Inactive	0.408	0.404
7. Active	0.386	0.389
Inactive	0.384	0.396
8. Active	0.401	0.404
Inactive	0.437	0.428
9. Active	0.425	0.401
Inactive	0.430	0.419
10. Active	0.381	0.367
Inactive	0.388	0.384

Six patients with inactive rheumatic fever in the group under study had a K of 0.430 or greater. These six cases were reviewed separately, and it was observed that four of the six had definite evidence of left ventricular hypertrophy. Two cases were considered to have no residual valvular or myocardial disease and were returned to duty.

Widely divergent results such as the literature records may result from many sources of technical error. Because the technique of measurement advocated by Taran and Szilagyi is so onerous, ten cases were selected at random from the rheumatic cases and measurements made by the technique recommended by these authors. These values were then compared with the results obtained by the method used for the entire group (Table I). It will be seen that in one of 20 determinations K varied 0.015, and it varied more than 0.010 in five. Concomitantly it is observed that only three of the ten cases had K values in excess of 0.420 during activity while a similar number had an elevation above this level at the time of discharge.

SUMMARY

1. The Q-T intervals in 200 healthy young adult men and 110 men with acute rheumatic fever were studied. Using the Bazett formula the mean K in controls was 0.383. During active rheumatic fever the mean K was 0.405, and following subsidence of rheumatic activity it was found to equal 0.400.

2. During rheumatic activity 26.3 per cent of patients had a K value in excess of 0.420, while only 3.5 per cent of the control group exceeded this level.

3. In sixty-eight cases K decreased with the disappearance of signs of rheumatic activity. In forty-two patients this value increased during convalescence.

4. Cardiac enlargement is suggested as one of the causes for K prolongation during the inactive phase of rheumatic fever.

5. In this age group, analysis of the Q-T interval by the technique described gave no assistance in assessing rheumatic activity.

SUMMARIO IN INTERLINGUA

Le valor que le corrigite duration Q-T del electrocardiogramma possede in determinar le activitate rheumatic es ancora de natura controverse.

Nos reporta un studio executate pro evalutar le signification del corrigite duration Q-T super le base de mesurationes in casos de acute febre rheumatic, de patientes clinicamente inactive sed convalescente ab ille morbo, e de un serie de subjectos de controlo.

Esseva constatate que in le gruppo de etate coperite per nostre studio, le corrigite duration Q-T non es uniformemente de valor in separar le casos active ab le casos inactive.

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THE INCIDENCE OF RHEUMATIC ENDOCARDITIS*

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IT IS extremely difficult for the clinician to determine the real incidence of rheumatic endocarditis. That is the reason for the considerable variations in recorded statements. I would like to express an opinion on the incidence of the rheumatic endocarditis and its resultant disturbance of valvular functions from the pathological anatomic viewpoint.

We have evaluated the routine post-mortem material of recent years with specific reference to cases where the valves were not destroyed, and in the microscopic examination we have above all searched for myocardial lesions which we might assume to be residuals of a previous perivascular rheumatic myocarditis.

While there is no question regarding the pathological character of the really pronounced valvular lesions, we must, in the case of the minimal lesions which are the specific subject of this study, definitely consider if these changes really are to be considered residuals of inflammations, or if they may be anatomic variants or perhaps sclerosis caused by age.

Two kinds of valvular changes must be considered valuable criteria, viz., the fusion of the commissure of the aortic valves and the cylindrical thickening or reticular fusions of the chordae tendineae of the mitral valves. There can be no doubt that these fusions are the results of previous inflammations. If these were congenital abnormalities they would not increase in frequency with advancing age and they are but rarely seen in children. It is unlikely that they represent sclerosis caused by mechanical stress, for it is unthinkable that two separate structures should fuse without previous inflammation. We agree with Böhmig and Klein in this interpretation[1] (Figs. 1 and 2). On microscopic examination we find where the commissures have been fused to a coarse, disorganized, collagenous connective tissue with few nuclei, in which reticular lattice fibers are missing and the elastic fibers are interrupted. Often nearby are small blood vessels which here and there are surrounded by round cells. Similar changes occur where the chordae fuse. We believe that these fusion areas represent residuals of previous rheumatic (allergic-hyperergic) endocarditides. While it is possible that sclerosis of the valves may result from a simple serous inflammation, a rheumatic origin is rendered more likely by the frequent concurrence of perivascular spindle-shaped collagenous scars which are the end results of rheumatic granulomata.

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Received for publication March 3, 1955.
*Translated from the German text.

In 500 unselected post-mortem examinations of persons over five years of age, we found in 307 (61 per cent) cases the previously mentioned criteria of a previous endocarditis. In 6 per cent of the cases there was an acute recurrent endocarditis and in 2 per cent an ulcerating inflammation of the heart valves together with old scarring. The mitral and aortic valves were affected with approximately equal frequency, but in the tricuspid valve we found only lesions nine times and then concurrent with corresponding changes in the valves of the left heart.

Fig. 1.

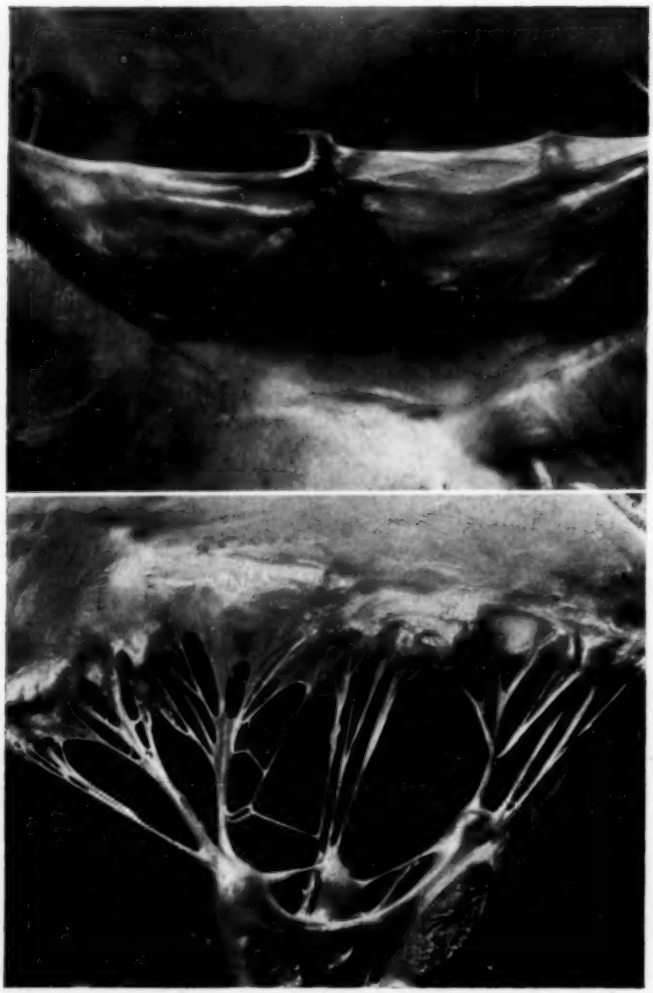

Fig. 2.

Fig. 1.—Mild fusion of the aortic valves.
Fig. 2.—Mild fusion of the chordae tendineae of the mitral valve.

However, of special interest is the fact that in 268 cases of unquestioned residuals of previous endocarditis without fresh recurrences or ulcerations, only 5.5 per cent had a real valvular defect of greater degree than could be explained by the destruction of the valve or the changes in the wall of the heart. On the

other hand, we found a valvular defect in 21 per cent of the cases of acute recurrent endocarditis and in 82 per cent of the cases of ulcerating inflammation.

When one examines the distribution of residual endocarditis over the various age groups, a great increase in the changes is noted between the ages of 20 and 25. From then on there is a steady increase, so that in the ninth decade evidence of endocarditis is found in 80 per cent of the hearts. Contary to this finding, others (Hall and Anderson[2]) have stated that the highest incidence is between 5 and 12 years of age. This discrepancy can be explained by the fact that these authors described endocarditis which had been diagnosed during life and not cases which were clinically silent and only discovered on the post-mortem table in the course of routine examinations. It is readily agreed that rheumatic endocarditis, which clinically has such a dramatic course and which often is followed by a valvular defect, is most frequent during the first three decades of life.

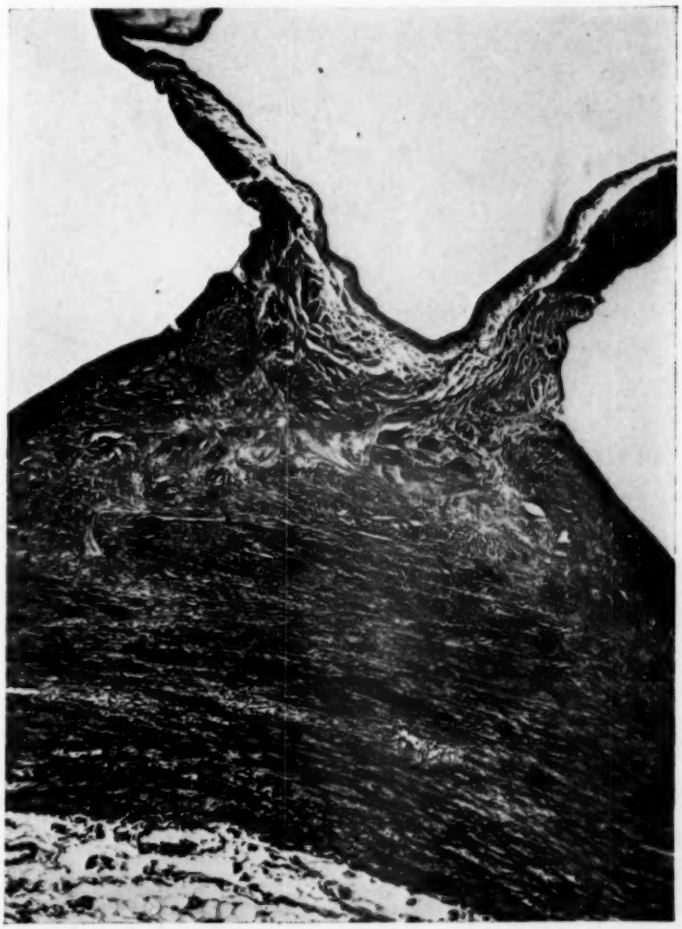

Fig. 3.—Fusion of the commissures of the aortic valves with definite scarring (× 32).

Our statistics show, nevertheless, an incidence of 20 per cent between the ages of 11 and 15. So it must be concluded that inflammations may affect valvular tissue even during the early years of life. As an example, I may cite a one-month-old female baby in which we noted as an accidental finding endocarditis

with a fresh granuloma derived from tissues of the mitral valve. In another case we noted in the mitral valve of a 14-year-old girl (who had died from poliomyelitis) an already well-developed granuloma in the immediate neighborhood of a new-formed vessel. This must then be a matter of rheumatic recurrence.

I considered it proper to mention these two cases because Böhmig and Klein[1] recently have emphasized the great rarity of fresh rheumatic granuloma in the valves, and that the lesion had never been found by numerous investigators.

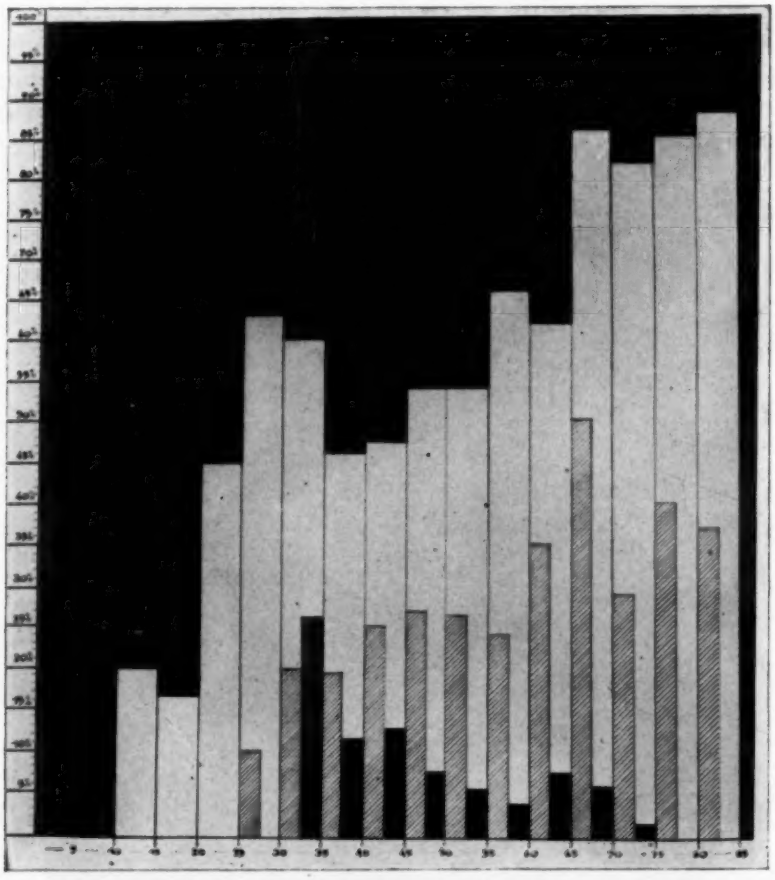

Fig. 4.—Age—distribution of the different residuals: White: endocarditis residuals without valvular defects; Black: valvular defects; Grey: rheumatic myocardial scars.

It is further of interest that in older people we have not been impressed by residuals of greater intensity of inflammation. This finding does not support the view that rheumatic endocarditis should have a great tendency to recur, even considering the possibility that a recurrence may at times run its course without a marked increase in anatomic change. This course is further rendered unlikely by the fact that the incidence increases statistically even into advanced age. If one assumes that a residual of endocarditis is the first stage of a developing valvular defect, then one must assume that in advanced age such traces become rarer and valvular defects more frequent, or that residual lesions on the whole decrease in frequency because patients with endocarditic scars will by then have

died from the resulting valvular defects. As this does not occur one is at least permitted to assume that the final healing of rheumatic endocarditis is the rule where the tendency to recurrence is slight.

Fig. 5.

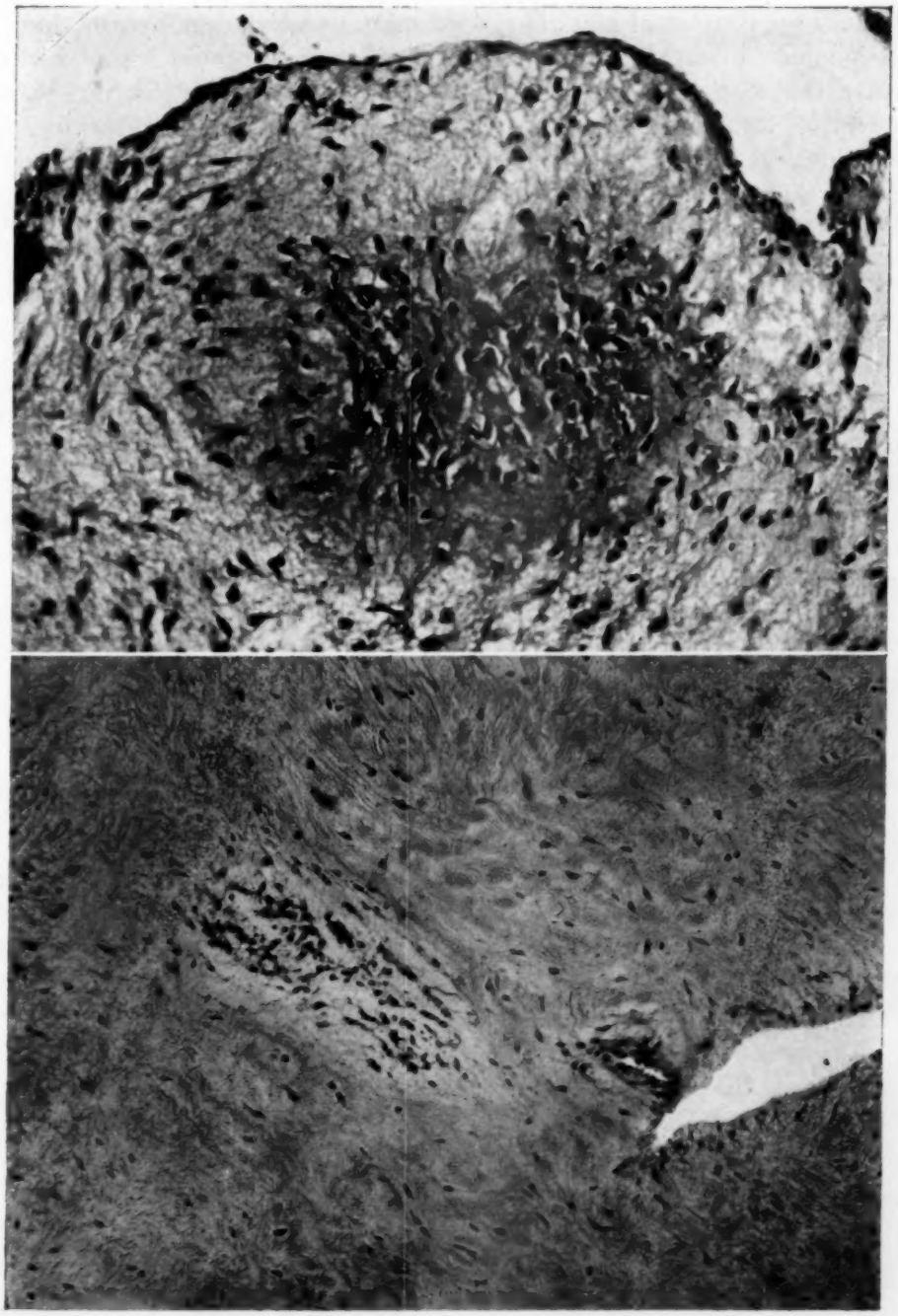

Fig. 6.

Fig. 5.—Fresh swelling with granulation in the mitral valve of a one-month-old baby (× 250).
Fig. 6.—Granuloma of a mitral valve. Rheumatic recurrence in a 14-year-old girl (× 132).

This opinion is in contrast to the views of many others who believe that endocarditis as a rule results in significant valvular defect and that functional healing is the exception.

Therefore, we come to the conclusion that rheumatic endocarditis is a very common pathological process, which generally escapes clinical observation. It may be a complication of any kind of infection which does not really deserve to be designated "disease." In such cases, it is rare to obtain a past history of articular rheumatism. The previously described anatomic findings have no considerable functional significance, and aggravating recurrences leading to valvular defects are rare. We believe, then, that these lesions represent allergic-hyperergic "rheumatic" endocarditis and mostly are clinically insignificant and have a favorable prognosis.

SUMMARIO IN INTERLINGUA

Super le base de 500 necropsias executate in le curso de plure annos le autor formula le sequente conclusiones:

Endocarditis rheumatic es un frequentissime processo pathologic que in le majoritate del casos elude le observation clinic. Illo pote occurrer como complication de omne genere de infection e alora non merita le nomine de "morbo." In tal casos il es rar que on obtene un historia de rheumatismo articular. Le tractos anatomic que characterisa le condition non possede ulle considerabile signification functional, e recurrentias aggravante que resulta in defectos valvular es rar. Es justificate le opinion que iste lesiones representa un endocarditis allergico-hyperergic. Illos es generalmente sin signification clinic e ha un prognose favorabile.

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PULMONIC STENOSIS WITH LEFT-TO-RIGHT VENTRICULAR SHUNT

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DURING the last few years the development of surgical techniques for the correction of pulmonic stenosis and its sequelae has greatly stimulated interest in this condition, especially that with a normal aortic root. Although this latter condition may take the form of isolated pulmonic stenosis with no communication between the greater and lesser circulations, it is more commonly associated with a defect of the atrial or ventricular septum. The right ventricular and atrial hypertension, which follows pulmonic stenosis, usually causes the blood to shunt from right to left. However, a few reports of left-to-right shunts have appeared in the literature.[2-7] Since this latter condition is rather uncommon and its clinical and hemodynamic manifestations, as well as the indications for its surgical correction, have not been clearly delineated, it was deemed advisable to report an additional eight cases studied in the Cardiovascular Department of the Michael Reese Hospital.

METHODS AND MATERIAL

These eight patients, ranging in age from 5 to 24 years, were selected from approximately 500 cardiac catheterization records. In all cases the analysis included a review of the history, physical examination, x-ray pictures, fluoroscopy, electrocardiogram, and cardiac catheterization data. The latter procedure was carried out in the routine manner.

All eight cases had (1) pulmonic stenosis, (2) a left-to-right shunt between the ventricles, (3) an oxygen increase from right atrium to ventricle of at least 1.1 volume per cent, (4) a pulmonary flow greater than the systemic, and (5) a systemic arterial oxygen saturation of at least 90 per cent. Since functional pulmonic stenosis has been reported to occur in patients with large left-to-right intracardiac shunts,[1] selection of the patients in this series was based upon the additional presence of a large pressure gradient between right ventricle and pulmonary artery.

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Aided by the Michael Reese Research Foundation and the National Heart Institute (grants H218 and HF 4658).

Received for publication Feb. 25, 1955.

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TABLE I. SUMMARY

CASE NO.	AGE (YR.)	TIME OF FIRST DIAGNOSIS	GROWTH AND DEVELOPMENT	CYANOSIS	CLUBBING	SQUATTING PRESENT?	DYSPNEA	MURMURS
1	24	Birth	Poor	Exertional	None	Yes	Mild on exertion	Grade III systolic, maximum in 2nd left I.C.S., widely transmitted
2	10	6 mo.	Normal	Exertional	None	Yes	Mild on exertion	Grade IV systolic, maximum in 2nd, 3rd, 4th left I.C.S.; widely transmitted
3	9	Birth	Normal	None	None	No	Mild on exertion	Grade IV systolic, maximum in 2nd left I.C.S.; widely transmitted
4	5	Birth	Normal	None	None	No	None	Grade III systolic, maximum in 2nd, 3rd, left I.C.S.; widely transmitted
5	9	9 mo.	Normal	None	None	No	None	Grade V systolic, maximum in 4th left I.C.S.; widely transmitted
6	7	2½ yr.	Normal	None	None	No	Moderate on exertion	Grade IV, systolic, maximum in left 2nd, and 3rd I.C.S.
7	24	Birth	Normal	None	None	No	Moderate on exertion	Grade IV systolic, maximum in pulmonic area; short early diastolic at Erb's point
8	9	9 mo.	Normal	None	None	No	Mild on exertion	Grade V systolic, maximum in 4th and 5th left I.C.S.; widely transmitted

Pulmonary flows (PF) and systemic flows (SF) were calculated by application of the direct Fick principle and expressed as a ratio (PF/SF).

RESULTS

Clinical Findings.—The salient clinical features in these patients are summarized in Table I. These patients showed normal development, absence of cyanosis at rest, reasonably good adaptation to the congenital anomaly, and absence of clubbing. The second pulmonic sound was markedly diminished or absent and there was a Grade 3 to 5 harsh systolic murmur, maximal over the second and third intercostal spaces at the left parasternal line, associated with a thrill in the same area.

OF CLINICAL DATA

THRILL	PULMONIC 2ND SOUND	X-RAY FINDINGS	ECG FINDINGS
None	Moderately diminished	Vascularity of lung fields normal; transverse diameter normal; left aortic arch	Sinus rhythm; P-congenitale; right-heart strain; incomplete R.B.B.S.B.
Systolic, maximum in 2nd, 3rd and 4th left I.C.S.	Absent	Vascularity of lung fields normal; transverse diameter normal; prominent L.M.S.; retrosternal encroachment; left aortic arch	Sinus rhythm; right-heart strain
Systolic, maximum in 2nd left I.C.S.	Markedly diminished	Vascularity of lung fields increased; fullness of L.M.S.; slight retrosternal encroachment; left aortic arch	Sinus rhythm; right-heart strain; incomplete R.B.B.S.B.
Systolic, maximum in 2nd, 3rd left I.C.S.	Markedly diminished	Vascularity of lung fields increased; transverse diameter increased; hilar dance; prominent L.M.S.; retrosternal encroachment; right aortic arch	Sinus rhythm; right-heart strain; incomplete R.B.B.S.B.
Systolic, maximum in 4th left I.C.S.	Diminished	Vascularity of lung fields normal; transverse diameter normal; prominent L.M.S.; retrosternal encroachment; left aortic arch	Sinus rhythm; right-heart strain; incomplete R.B.B.S.B.
Systolic, maximum in 2nd and 3rd left I.C.S.	Markedly diminished	Vascularity of lung fields normal; transverse diameter normal; hilar dance; left aortic arch	Sinus rhythm; right-heart strain; complete R.B.B.S.B.
Systolic, maximum in 2nd left I.C.S.	Absent	Vascularity of lung fields slightly increased; transverse diameter increased; hilar dance; prominent L.M.S.; retrosternal encroachment; right aortic arch	Sinus rhythm; right-heart strain; incomplete R.B.B.S.B.
Systolic, maximum in 2nd, 3rd and 4th left I.C.S.	Markedly diminished	Vascularity of lung fields normal; transverse diameter normal; retrosternal encroachment; left aortic arch	Sinus rhythm; right-heart strain

I.C.S.—Intercostal space; L.M.S.—Left middle salient; R.B.B.S.B.—Right bundle branch system block.

X-rays revealed normal or increased vascularity of the lung fields, often associated with dilatation of the main branches of the pulmonary artery and enlargement of the outflow tract of the right ventricle.

The electrocardiogram showed right-heart strain, usually associated with incomplete right bundle branch system block.

It should be noted that Cases 1 and 2 became cyanotic during exercise; the arterial oxygen saturation dropping from 90 to 65 per cent in Case 1 and from 90 to 50 per cent in Case 2. Cases 4 and 5 had no history of dyspnea on effort, and the systolic murmur in Cases 5 and 8 was maximal over the fourth and fifth left intercostal spaces parasternally. Only in Case 1 was the physical development below normal. Cases 6 and 7 showed hilar dance on fluoroscopy.

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TABLE II. SUMMARY OF CATHETERIZATION DATA

CASE NO.	AGE (YR.)	OXYGEN CONTENT (VOL. %)								PRESSURE (MM. HG)*							PF/SF
		IVC	SVC	RA	RV	PA	LV	AO	BA	RA	RV	INF.	PA	LV	AO	BA	
1	24	14.8	15.1	14.7 15.1 14.8	17.2 17.3	16.8 17.0 17.4	—	—	20.6‡ (90%)	2	82/0	65/0	6	—	—	102/60	1.2
2†	10	14.4	12.7	13.5 13.6 13.8	14.7	14.9 15.6 15.7	—	—	17.9‡ (90%)	0	100/5	25/5	10	—	—	75/58	1.3
3†	9	13.1	11.6	11.5 12.4 12.5	13.2 14.0	14.0 14.4 14.2	—	16.9 (94%)	—	0	95/0	23/0	23/6	—	95/62	—	1.6
4†	5	10.0	8.7	8.9 9.7	11.6 11.4	12.8 11.7	14.1	14.0 (95%)	—	0	65/0	—	20/10	90/5	90/65	—	3.0
5†	9	12.5	10.8	10.5 10.8 11.0	13.0 13.3	13.0	17.0 (95%)	—	—	0	70/2	15/2	13/5	—	—	110/56	1.5
6†	7	11.5	10.2	10.9 9.3 9.9	14.1	14.1 13.8	16.2 (96%)	—	—	3	75/5	—	22/5	—	—	98/64	2.6
7†	24	13.3 13.4	13.0	12.5 13.5 13.2	14.7 16.4	14.1 15.4	—	—	18.6 (94%)	2	100/5	—	30/5	—	—	100/70	1.4
8	9	11.6	10.9	11.4 11.4	16.7 16.6 14.1	14.7 14.8 14.8	—	—	17.1 (95%)	—	105/5	55/5	40/15	—	—	100/60	2.3

*Single number represents mean pressure.
†Oxygen consumption assumed to be 100 c.c./minute.
‡During exercise O_2 saturation fell to 67 and 50 per cent in Cases I and II.

IVC—Inferior vena cava
SVC—Superior vena cava
RA—Right auricle
RV—Right ventricle
PA—Pulmonary artery
LV—Left ventricle
Ao—Aorta
BA—Brachial artery
Inf.—Infundibular chamber of right ventricle
PF/SF—Ratio of pulmonic (PF) over systemic flow (SF)

Hemodynamic Findings.—The pertinent data are summarized in Table II. It was found that the ratio PF/SF varied from 1.2 to 3.0 : 1. The smallest ratios were observed in Cases 1 and 2, where a bidirectional shunt was present (as indicated by the lowered systemic arterial oxygen saturation). In these cases the left-to-right shunt between the ventricles was greater than the values of pulmonary flow would lead one to believe, because part of the right ventricular volume was shunted into the systemic circuit.

The pressure gradient between the right ventricle and the pulmonary artery (ranging from 45 to 85 mm. Hg) was sufficiently large in all cases to confirm the presence of severe pulmonic stenosis. In all cases the right ventricular pressure tended to approach the systemic pressure. Five patients had evidence of infundibular type of pulmonic stenosis.

DISCUSSION

It has been rather difficult to establish criteria for the diagnosis and therapy of pulmonic stenosis with left-to-right ventricular shunt, because of the relative rarity of the condition. Fifteen well-established cases, along with eleven others, where the diagnosis is questionable, have been published[2-7]; the present report adds eight more.

The patients in our series apparently adapted quite well to the congenital anomaly, having had normal development, fairly good exercise tolerance, and absence of cyanosis and clubbing. In these cases in contrast to patients with pulmonic stenosis and right-to-left shunt, the vascularity of the lung fields is normal or increased. In the presence of the typical murmur of pulmonic stenosis and markedly diminished or absent second pulmonic sound, this finding should lead one to consider an associated left-to-right intracardiac shunt. The electrocardiogram presents evidence of resistance to right ventricular ejection (right-heart strain) in all cases and of input overloading (right bundle branch system block),[8,9] presumably the result of the left-to-right shunt in six cases. Therefore, six patients had evidence of both input and output type of right-heart strain ("combined right heart strain"). Thus, when a right-sided conduction defect is superimposed on a right-heart strain it may suggest an intracardiac left-to-right shunt coexistent with an augmented resistance to right ventricular ejection.

When pulmonic stenosis is associated with ventricular septal defect, there is usually a right-to-left shunt, the right ventricular pressure being high enough during part of the heart cycle to pump blood across the defect into the left ventricle and aorta. However, if the aorta overrides, the right ventricle may also be able to overcome aortic diastolic pressure and pump some blood directly into the aorta even in the presence of a left-to-right ventricular shunt. The presence of a left-to-right shunt signifies that the volume-elasticity characteristics of the ventricles are such that it is easier to eject blood into the pulmonary artery than into the aorta. The shunt may exist without change in the relationship of pulmonary and systemic resistance or may result from enhanced resistance to left ventricular ejection either at the aortic orifice or in the systemic arterioles,

PF/SF—Ratio of pulmonic (PF) over systemic flow (SF)

PA—Pulmonary artery

or, if the pulmonic stenosis is not severe enough, to result in a marked elevation of right ventricular pressure. Any fall in systemic pressure, such as may occur during exercise, anxiety, severe bradycardia, arrhythmias during cardiac catheterization, administration of hypotensive drugs, or from postural hypotension or shock due to blood loss, may be sufficient to cause reversal of the shunt[10] with by-passing of the lungs and rather marked cyanosis. Therefore, under one set of conditions, the patient will have pulmonic stenosis with left-to-right ventricular shunt, while under other conditions there will be a right-to-left shunt.

Clinically, patients with the tetralogy of Fallot have right-to-left shunt with cyanosis and clubbing. The crucial difference in the series reported here is that there is left-to-right shunting of blood and cyanosis is absent. Although there are no anatomic data about overriding in this series, physiologic overriding may occur even when the anatomic diagnosis is questionable. For example, Cases 1 and 2 may be considered to have physiologic overriding because a small right-to-left shunt existed in the presence of a left-to-right shunt between the ventricles. At rest these patients have a left-to-right shunt and during exercise they exhibit a right-to-left shunt, such as is characteristic of the tetralogy of Fallot. However, the six other patients had no evidence of any right-to-left shunt. Abrahams and Wood[2] report one patient in whom pulmonic stenosis and a left-to-right ventricular shunt were present with a systemic arterial oxygen saturation of 91 per cent. This patient became intensely cyanosed later in life and at autopsy showed the typical findings of tetralogy of Fallot. The question arises whether the cases with left-to-right shunt are in reality unrecognized tetralogy of Fallot who may develop right-to-left shunt in the future and then show the classical features of tetralogy.

There are two general surgical approaches to pulmonic stenosis associated with ventricular septal defect, a shunting procedure, such as advocated by Blalock and Potts, and pulmonic valvotomy. In these patients the former procedure is not practical, because pulmonary flow is normal or increased, and there is no problem of poorly oxygenated systemic arterial blood. Pulmonic valvotomy also is of questionable value since it is impossible to estimate the size of the ventricular septal defect prior to surgery. In the presence of a large ventricular septal defect with left-to-right shunt, relief of pulmonic stenosis may produce a left-to-right shunt of tremendous magnitude, actually causing the patient to bleed as it were into his lungs and die in shock. Therefore, the clinician is presented with a therapeutic dilemma.

Cases 1 and 2, who exhibited considerable right-to-left shunts during exercise, might possibly benefit from surgery. But in the other six patients pulmonic valvotomy might so magnify the left-to-right shunt that they would be worse off than previously.

Since patients like those reported usually tolerate their congenital anomaly quite well, it would appear to be wiser to await the future development of more practical surgery for septal defect.

SUMMARY AND CONCLUSIONS

1. Eight patients with pulmonic stenosis and left-to-right ventricular shunt are reported.

2. The salient clinical features were normal development, absence of cyanosis at rest, reasonably good adaptation to the congenital anomaly, and absence of clubbing. The vascularity of the lungs was normal or increased, even when the second pulmonic sound was markedly diminished or absent, and the classical murmur of pulmonic stenosis was heard. The electrocardiogram showed right-heart strain, usually associated with evidence of right bundle branch system block.

3. The clinician is faced with a therapeutic dilemma: (1) because pulmonic valvulotomy and/or infundibular resection, by producing a greater left-to-right shunt, may be deleterious; and (2) because shunting procedures are not necessary since the patient is acyanotic and has a good pulmonary flow.

4. Patients in this group, because of the reasonably good adaptation to their congenital anomaly, should await the development of more practical septal surgery.

SUMMARIO IN INTERLINGUA

1. Es reportate 8 patientes con stenosis pulmonic e sinistro-dextere derivation ventricular.

2. Le saliente characteristicas clinic esseva: disveloppamento normal, absentia de cyanosis in stato de reposo, adaptation satis perfecte al condition de un anomalia congenite, e absentia de digitos hippocratic. Le vascularitate del pulmones esseva normal o hypernormal, mesmo quando le secunde sono esseva marcatemente diminuite o absente e quando le classic murmure de stenosis pulmonic esseva audibile. Le electrocardiogramma monstrava effortio dextero-cardiac, usualmente in association con signos de bloco de branca dextere.

3. Le clinico se trova in tal casos ante un dilemma therapeutic. De un latere, valvulotomia pulmonic e/o resection infundibular producerea un augmentate derivation sinistro-dextere con effectos possibilemente damnose. Del altere latere, le operation derivational non es necessari proque le patiente es acyanotic e ha un bon fluxo pulmonar.

4. Patientes de iste categoria—in tanto que illes es characterisate per un satisfacente grado de adaptation a lor congenite anomalia—deberea attender le disveloppamento futer de formas plus practic de chirurgia septal.

The authors wish to acknowledge the indebtedness to Drs. Louis N. Katz and Aaron Shaffer for advice in the preparation of this manuscript.

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THE EFFECTS OF AGE ON FINGER TEMPERATURE RESPONSES TO LOCAL COOLING

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THE effects of local cold on the circulation through the fingers have been studied by Lewis[1] employing the skin temperature to measure the response. After 5 to 10 minutes immersion in water below 15° to 18° C., repeated transient skin temperature rises of a few degrees centigrade occurred, indicating periods of vasodilatation. These responses have been termed the hunting reaction. Similar studies have been made by Greenfield and Shepherd[2] and Edholm[3] with a more sensitive technique confirming in general the earlier observations of Lewis. Considerable variation has been noted in the development of this phenomena but the exact causative factors have not been elucidated. In the course of studies on finger blood flow in children it was observed that the occurrence of the hunting reaction disappeared when these studies were repeated on these same children at a later date. The possibility that the age of the individual might have some bearing on this phenomena was therefore considered, and this report is concerned with such studies on individuals of different chronological ages.

METHODS

Local cold immersion tests were conducted on four groups of subjects. The first group (I) consisted of two males and two females ranging in age from 6 to 7 years with a mean age of 6.5 years. These same individuals are also included in group II which had six males and six females ranging in age from 8 to 10 years with a mean age of 9.3 years. The third group (III) was composed of young adults, six males and two females, ranging in age from 22 to 31 years with a mean age of 24.4 years. The last group (IV) was made up of old males, 67 to 83 years in age, and having a mean age of 75.6 years.

The subjects were seated comfortably in a quiet, pleasant room having an ambient temperature of 27° ± 1° C. and a relative humidity of 50 per cent. The variation in ambient temperature during any experiment was within ± 0.3° C. Copper-constantan thermocouples were placed on the chest, upper arm,

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Aided in part by a grant from the Josiah Macy, Jr., Foundation, New York, N. Y.

This work was done during the tenure of a Research Fellowship of the American Heart Association.

Received for publication March 1, 1955.

thigh, calf, both large toes, and index fingers of both hands. Similar thermocouples were employed in determining the room, wall, and water bath temperatures. These temperatures were recorded continuously by means of Brown recording potentiometers (16 or 36 leads) having a sensitivity of 0.05° C. Calibration of the thermocouples was made against a Bureau of Standards thermometer at frequent intervals.

Control observations were made for a period of 30 minutes and then the right hand of the subject was immersed to the wrist in a stirred water bath having a temperature of 10° C. This temperature was constant during an experiment but varied ± 1° C. in different experiments. The duration of immersion varied in the four groups from 10, 20, and 30 minutes for the aged, the children, and young adults, respectively. The short duration of exposure for the oldest subjects was limited by their inability to tolerate further immersion without pain. At the conclusion of this period the hand was lifted from the bath, placed on a towel, lightly blotted to remove droplets of water and replaced on the arm of the chair. Temperature measurements were continued for an additional 20 to 30 minutes.

The data from these experiments were analyzed for the occurrence of "hunting reactions," cooling and rewarming rates. The curves obtained when the temperatures of the rewarming fingers were plotted against time, have the general form:

$$Y = 10^{a+kx} + C$$

where a, k, and C are constants, Y is temperature in °C. and x is time in minutes. These curves were rectified to fit a straight line and the slopes calculated by the method of least squares. The slopes thus determined were indicative of the over-all rewarming rate. Statistical treatment of the data was made on the basis of unpaired samples. The null hypothesis was rejected at the 5 per cent level.

RESULTS

Since no changes consequent to the cold immersion could be detected in the temperature measurements at other sites, the alterations in response of the immersed hand will only be considered. The average right index finger temperature prior to immersion of the right hand was 32.8° C. for subjects in each of the four groups. The data obtained during and following hand immersion in cold water are summarized in Table I.

The criterion for the presence of the hunting response was quite liberal, a temperature swing of 1° C. being considered as one cycle. The hunting reaction was observed in five of the six tests made on group I, two of the twelve tests in group II, five of eight tests in group III, and zero of nine tests in group IV. The four subjects of group I were restudied 3 years later as part of group II. Only one of these exhibited hunting reactions when they were older. Fig. 1 illustrates the pattern of this response in A.M.H. when she was 6.5 and 9.5 years old. The frequency of these cyclic vasodilatation phenomena was greater in

TABLE I. "HUNTING" PHENOMENA, COOLING AND REWARMING RATES OF FINGERS EXPOSED TO COLD WATER IN INDIVIDUALS OF DIFFERENT AGE GROUPS

GROUP	MEAN AGE (YR.)	MAGNITUDE OF CYCLES °C.		TIME TO FIRST CYCLE MIN.		COOLING RATE* °C./MIN.		REWARMING RATE† °C./MIN.		SLOPE OF REWARMING CURVE	
		MEAN	S. D.	MEAN	S. D.	MEAN	S. D.	MEAN	S. D.	MEAN	S. D.
I	6.5	8.3	2.6	2.0	0.0	10.4	0.8	2.2	1.3	0.2174	0.30
II	9.3	3.0	0.6	5.5	0.5	9.9	1.7	2.0	0.8	0.0470	0.03
I & II						10.0	1.5	2.0	0.9	0.0896	0.16
III	24.4	4.7	1.7	7.0	2.7	7.1	1.9	1.2	0.5	0.0444	0.08
IV	75.6	—	—	—	—	8.0	2.3	1.3	0.7	0.0409	0.03

*During first 2 minutes.
†During first 5 minutes.

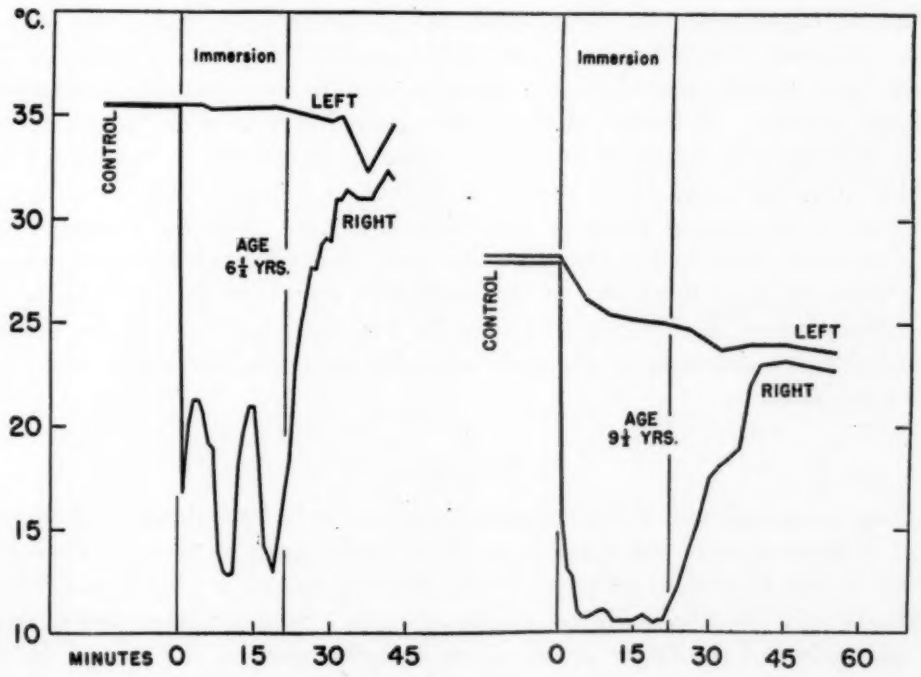

Fig. 1.—Finger temperatures obtained in a female subject at age 6.5 and 9.5 years before, during, and after immersion of right hand in a water bath of 9.5° C.

the very youngest group despite a relatively shorter period of cold immersion. In none of the subjects 8 to 10 years old were there more than two such cycles and usually only one during the half hour the hand was kept in cold water. The occurrence of the first cycle was significantly earlier in the youngest group. The magnitude of the vasodilatation as suggested by the extent of the temperature fluctuations was much greater for the 6 to 7-year-old subjects. In the older subjects the variations were considerably less.

The cooling and rewarming rates were measured over short time intervals in order to obtain information on the maximum speeds of these adjustments. Both cooling and rewarming rates were significantly more rapid in the two youngest group of subjects. No differences were observed between the young adults and the aged individuals. The slope of the entire rewarming curves (k) showed no statistically significant difference between any of the groups.

DISCUSSION

The hunting reaction is a variable phenomena in that no rhythm of alternating vasoconstriction and vasodilatation need occur and at times nothing but vasoconstriction is seen despite very long periods of cold immersion. Furthermore, in adjacent fingers one may be exhibiting the phenomena while the others remain completely vasoconstricted. The vasodilator response to cold may be due to an axon reflex[1] although Greenfield and Shepherd[2] have shown that it can occur independently of a nerve supply. In view of the difficulties of explaining the phenomena the demonstration that this response occurs relatively more frequently and with greater sensitivity in younger individuals than in the aged does not necessarily indicate a causative relation to the aging process. However, these results in conjunction with Jepson's[4] observation that reactive hyperemia does not develop as readily in the cooled hand of older individuals, 40 to 59 years, as it does in younger subjects is at least suggestive of changes in vascular reactivity with age. The more rapid cooling and rewarming rates of the children also tend to favor such an interpretation. The altered vascular reactivity of the small skin vessels in the older individuals to sudden changes in environment may be due to either (a) a more intensive vasoconstrictive response to the cold stimulus or (b) a decreased response to vasodilator stimuli.

SUMMARY

Finger temperature measurements were made before, during, and after a period of immersion of the hand in a 10° C. water bath on healthy individuals varying in age from 6 to 83 years. The hunting reaction tended to occur less frequently with the advancing age of the subjects. Similarly the rates of cooling and rewarming of the finger appeared to be influenced by the age of the individual. It is suggested that these differences in response to a local cold stimulus were related to changes in vascular reactivity.

SUMMARIO IN INTERLINGUA

Mesurationes del temperatura digital esseva executate ante, durante, e post le immersion del mano in un banio de aqua de 10 C in normal individuos de etates inter 6 e 83 annos. Le repetite e transiente augmentos del temperatura dermatic per alicun grados que ha essite observate in tal experimentos post immersiones durante 5 o 10 minutas e que es cognoscite como "le reaction chassante," tendeva a occurrer minus frequentemente con le etate avantiante del

individuo studiate. Similemente le rapiditate del abassamento e del realtiamento del temperatura digital pareva influentiate per le etate del subjecto. Nos opina que iste differentias in le responsa a stimulos local de frigor es conditionate per differentias del reactivitate vascular.

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THE EFFECT OF ORAL 1-HYDRAZINOPHTHALAZINE THERAPY ON RENAL FUNCTION IN ESSENTIAL VASCULAR HYPERTENSION

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MANY new drugs have been introduced recently for the treatment of essential vascular hypertension.[1-5] It is obvious that these drugs must not only lower the blood pressure significantly but must do so without compromising the blood flow to the vital organs. It would seem preferable to use a drug or combination of drugs which would increase the effective circulation to the kidneys, since renal blood flow is decreased relatively early in the course of essential hypertension leading to partial ischemia of the remaining functional tubular tissue.[6] Numerous acute hemodynamic studies have been reported in which 1-hydrazinophthalazine was found to not only lower the blood pressure significantly, but also to increase the effective renal blood flow.[7-10] The cardiac output was also increased in many of these acute studies,[8-10] and it was possible for the renal blood flow to have increased in conjunction with this factor alone. Since these results do not necessarily reflect changes which might occur during prolonged oral therapy, the present study was undertaken to determine the effect of orally administered hydrazinophthalazine* combined with subcutaneous injections of hexamethonium* on the blood pressure, renal hemodynamics, and the resting cardiac output in severe and early malignant essential hypertension.

METHODS AND MATERIALS

Fourteen patients with severe essential hypertension were studied. There were five males and nine females. The ages ranged from 32 to 59 years. All patients were hospitalized for study and treatment and received a complete history and physical examination. Laboratory examinations included a chest x-ray, intravenous pyelogram, electrocardiogram, Regitine test, phenolsulfonphthalein excretion test, complete blood count, urinalysis, and routine blood chemistry determinations. The blood pressure of all patients was over 230 mm. Hg systolic and 140 mm. Hg diastolic at the time of admission to the hospital.

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This work was supported in part by grants from the Michigan Heart Association and the National Institutes of Health.

Received for publication Feb. 25, 1955.

*1-Hydrazinophthalazine (Apresoline) used in this study was generously supplied by Dr. F. L. Mohr of Ciba Pharmaceutical Products, Inc., and the injectable hexamethonium (Bistrium) by Dr. A. Dale Console of E. R. Squibb & Sons.

The ocular fundi were Graded as 3 or 4 (Keith-Wagener classification) in twelve patients and as Grade 2 in two. Two of the group (HW and JB) showed marked sclerotic changes of the arterioles. The initial blood urea nitrogen was over 25 mg./100 c.c. in three patients. Eight patients had signs or symptoms referable to the central nervous system as complications of their hypertension, while six had a mild to moderate degree of congestive heart failure on admission. In no case could a definitive cause for the hypertension be found.

All patients were placed at bed rest before institution of antihypertensive therapy. This period was at least two weeks in duration in twelve of the patients, but because of clinical urgency the period of control observation was shortened to seven and twelve days in two patients (BMc and AC). Patients with congestive heart failure were recompensated with the usual cardiac regimen which included digitalization, dietary restriction of sodium, and diuretics when necessary. The diet varied from one containing 200 mg. of sodium per day to the regular house diet and was kept constant for each patient throughout the period of study.

Blood pressures were recorded twice daily at approximately the same hours by the same examiner. The average control blood pressure was obtained after the initial decrease occurring with bed rest alone and during the last seven days prior to institution of drug therapy (Table I). The average blood pressure after therapy was obtained during the last seven days of maximum therapy. The mean blood pressure was calculated as the average diastolic pressure plus one-third of the pulse pressure.

After the blood pressure had become stabilized with bed rest, specific renal function studies were done and antihypertensive drug therapy was started. Hexamethonium was administered subcutaneously every six hours starting with 3 or 5 mg. doses. This amount was gradually increased to a maximum total of 20 to 100 mg. per day. Hydrazinophthalazine was administered orally at the same time beginning with 25 mg. doses and increasing gradually to a maximum total of 400 to 900 mg. per day. One patient (AMc) received hydrazinophthalazine only.

The glomerular filtration rate (GFR), renal plasma flow (RPF), and maximum tubular excretory capacity (Tm_{PAH}) were measured by the renal clearances of inulin and para-aminohippurate.[11] The measurements were made immediately before institution of hydrazinophthalazine-hexamethonium therapy and again after 14 to 41 days of such treatment. The values for these functions represent the average of at least three 10-minute collection periods. Analyses for each collection period were required to check within 10 per cent of each other. All values were corrected to 1.73 $M.^2$ body surface area.

Cardiopulmonary hemodynamic studies were done in conjunction with the renal function studies in four patients utilizing the technique of cardiac and renal vein catheterization.* The cardiac output was determined by the direct Fick method. Renal resistances were calculated from the formulas derived by Gomez (quoted in Smith[6]).

*The authors are indebted to Dr. Harper K. Hellems for assistance in this part of the study.

TABLE I. THE EFFECT OF HYDRAZINOPHTHALAZINE-HEXAMETHONIUM THERAPY IN ESSENTIAL VASCULAR HYPERTENSION

PATIENT	COMPLICATION ON ADMISSION	BLOOD PRESSURE			MEAN BLOOD PRESSURE (MM. HG)		FUNDI (K-W CLASS.)	MAXIMUM DOSE OF HEXAMETHONIUM (MG./DAY)	MAXIMUM DOSE OF HYDRAZINOPHTHALAZINE (MG./DAY)
		ADMISSION (MM. HG)	PRETHERAPY (MM. HG)	THERAPY (MM. HG)	PRETHERAPY	THERAPY			
BMc	CNS	236/160	235/178	180/118	197	138	IV	20	500
PE	CHF	280/160	237/140	187/107	172	133	III	40	400
MM	CNS	250/140	222/119	222/119	153	153	II	60	600
JB	CNS	240/140	209/123	170/99	151	122	III	40	400
HW	CHF	210/146	191/112	190/102	138	132	II	80	600
AC	CHF CNS	240/140	204/131	165/109	155	127	III	60	600
MT	CNS	300/180	174/116	149/98	135	115	III	40	600
JG	CHF	240/130	206/115	154/97	145	117	III	20	400
SL	CHF	240/130	194/125	171/115	148	133	III	40	400
SP	CNS	234/130	235/127	207/112	163	144	IV	100	600
WM	CNS	300/140	252/146	190/113	181	139	IV	80	600
HS	CHF	250/170	212/146	190/113	168	150	III	40	400
AMc	CNS	230/158	190/146	159/117	161	131	III	—	900
AD	CNS	250/150	201/138	184/121	159	142	III	40	600

RESULTS

All patients tolerated the antihypertensive drugs well and experienced moderate to marked subjective improvement as their hypertension was relieved. Toxic side effects were minimal and were limited to mild constipation which was relieved by milk of magnesia and fluid-extract of cascara sagrada. The absence of troublesome side effects was probably related to the low initial dosages used, the simultaneous administration of the two antihypertensive agents, and the gradual stepwise increase in dosage to an effective level.

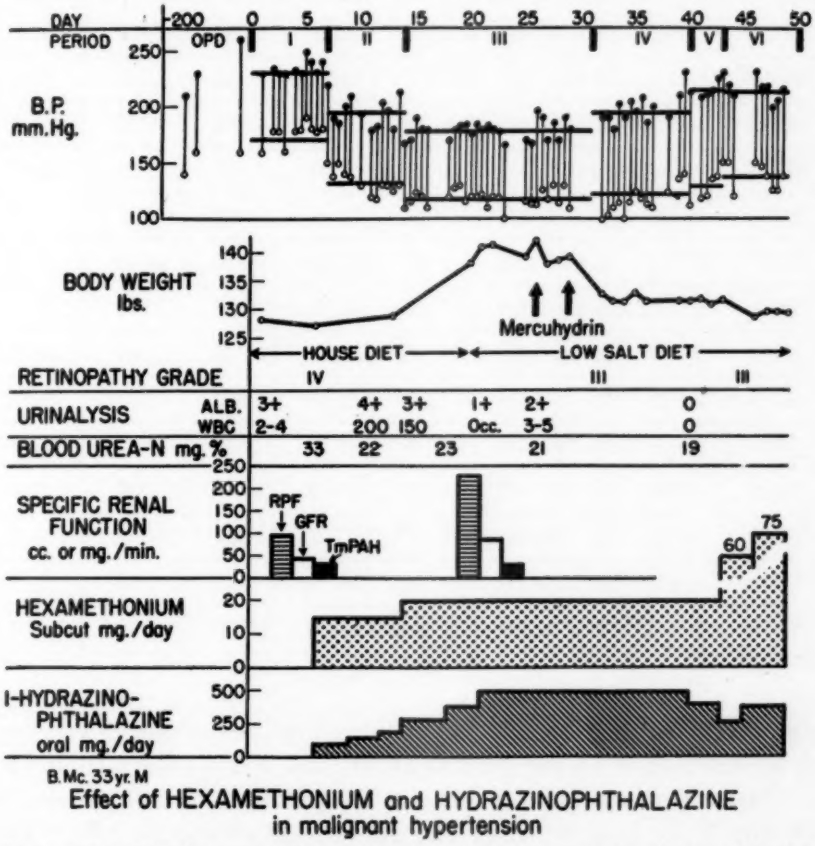

Fig. 1.—The clinical course of patient B.Mc.; malignant hypertension treated with hydrazinophthalazine and hexamethonium.

Twelve patients showed a blood pressure fall of at least 20 mm. Hg systolic or 15 mm. Hg diastolic pressure (Table I). Two patients (MM and HW) had essentially no change in their blood pressure from the antihypertensive therapy. The mean blood pressure decreased at least 15 mm. Hg in the previously mentioned twelve patients and ranged from 15 to 59 mm. Hg (Table I). One of the patients who showed no blood pressure response had marked arteriosclerosis (HW). In no case did the blood urea nitrogen concentration increase.

The effective renal plasma flow increased by 35 per cent or more in seven patients after hydrazinophthalazine-hexamethonium therapy, and by 21, 19, and 14 per cent in three (Table II). Two patients with significant arteriosclerosis showed no appreciable change. In two cases the renal plasma flow decreased by 14 and 42 per cent.

TABLE II. THE EFFECT OF HYDRAZINOPHTHALAZINE-HEXAMETHONIUM THERAPY ON

PATIENT	GLOMERULAR FILTRATION RATE (C.C./MIN.)		EFFECTIVE RENAL PLASMA FLOW (C.C./MIN.)		Tm_{PAH} (MG./MIN.)		FILTRATION FRACTION (%)		RBF/Tm_{PAH} (C.C./MG.)	
	PRE-THERAPY	THERAPY	PRE-THERAPY	THERAPY	PRE-THERAPY	THERAPY	PRE-THERAPY	THERAPY	PRE-THERAPY	THERAPY
BMc	46	77	101	227	30	28	46	37	6.8	13.2
PE	16	17	50	100	13	10	32	17	6.0	15.5
MM	92	94	282	393	68	67	33	24	7.5	10.4
JB	84	60	360	387	61	57	21	16	9.6	10.5
HW	61	44	246	266	51	56	25	17	7.6	7.8
AC	74	83	163	275	51	50	45	30	5.3	9.2
MT	83	91	369	504	53	59	23	18	11.6	13.7
JG	87	103	275	379	48	44	32	27	11.0	16.2
SL	82	115	162	231	30	36	51	50	11.1	12.9
SP	71	51	279	162	34	35	25	32	13.9	7.7
WM	39	34	111	127	21	8	35	27	11.0	24.4
HS	87	90	283	244	47	37	31	37	10.3	10.1
AMc	67	73	317	377	60	59	21	19	10.1	10.4
AD	83	71	258	311	56	42	32	23	7.4	12.5

The glomerular filtration rate showed no significant change in eight patients, increased by more than 15 per cent in three, and fell by more than 15 per cent in three. The filtration fraction fell over 20 per cent in eight cases, decreased by 19, 14, and 8 per cent in three and showed no change in one. Two others manifested an increase in the filtration fraction of 20 and 29 per cent.

Maximum capacity of the tubules to excrete para-aminohippurate (Tm_{PAH}) did not change significantly in twelve cases and decreased somewhat in two (Table II). The ratio of renal blood flow to the maximum tubular capacity (RBF/Tm_{PAH}) was increased by over 15 per cent in nine patients but was not significantly altered in the other five. Changes in cardiac output, measured in four patients, were negligible, and could not be correlated with changes in renal blood flow. The renal extraction of PAH was within normal limits in the four patients studied.

The calculated total renal resistance decreased by 15.2 to 62.4 per cent in twelve patients and increased by 13.9 and 51.7 per cent in two (Table II). In terms of per cent change and in absolute values the greatest fall in renal resistance was accounted for by decreases in the afferent arteriolar resistance.

RENAL FUNCTION AND RENAL RESISTANCES IN ESSENTIAL VASCULAR HYPERTENSION

CARDIAC OUTPUT (LITERS/MIN.)		TOTAL RENAL RESISTANCE (DYNES.SEC.CM.$^{-5}$)		VENULAR RESISTANCE (DYNES.SEC.CM.$^{-5}$)		EFFERENT RESISTANCE (DYNES.SEC.CM.$^{-5}$)		AFFERENT RESISTANCE (DYNES.SEC.CM.$^{-5}$)	
PRE-THERAPY	THERAPY	PRE-THERAPY	THERAPY	PRE-THERAPY	THERAPY	PRE-THERAPY	THERAPY	PRE-THERAPY	THERAPY
		72608	27125	9623	5298	4722	4206	58740	18479
		167638	65338	25870	13280	4720	2127	138457	50198
		22508	16231	3952	2838	3627	2545	15699	11203
9.75	7.23	19042	15000	3376	3348	2720	1834	13343	10004
		26560	22337	5187	4569	3073	1813	18779	16082
		42633	20311	7351	4340	6099	3583	30814	13019
		16169	10240	3234	2438	2537	2046	10736	5978
4.35	4.06	20661	11957	3816	2794	3287	2747	14074	6817
2.80	3.10	33120	20852	6000	4238	5440	5302	23088	12613
6.02	5.78	26161	39692	4275	7405	2926	3853	19390	29206
		60023	50140	8775	9717	3422	3303	48440	37702
		26393	30068	4176	5369	3641	5209	19243	20747
		19854	15780	3287	3260	2025	2206	16081	10563
		28957	19958	4859	3780	4181	2541	20795	13970

The clinical courses of three representative cases are illustrated in Figs. 1, 2, and 3. Patient BMc (Fig. 1), a 33-year-old Negro, was admitted with encephalopathic symptoms of headache, dizziness, and confusion. He was started on drug therapy after only seven days of observation because of the seriousness of his condition and refractoriness to bed rest and nonspecific measures. The initial response was excellent with clearing of the sensorium and relief of the headache. The blood pressure fell from an average of 236 mm. Hg systolic and 160 mm. Hg diastolic to an average of 190 mm. Hg systolic and 130 mm. Hg diastolic during the first week of therapy, and then to 180 mm. Hg systolic and 118 mm. Hg diastolic during the second, third, and part of the fourth week of therapy. Five hundred mg. of oral hydrazinophthalazine and 20 mg. of subcutaneous hexamethonium per day were necessary to attain this degree of improvement. Subsequently, in spite of greater doses of hexamethonium, the blood pressure control became less marked. Retinopathy, however, continued to improve and the malignant nature of the disease reverted to a state of benign hypertension. The effective renal plasma flow rose from 101 to 227 c.c. per minute, and the glomerular filtration rate increased from 46 to 77 c.c. per minute. There was no essential change in the Tm_{PAH}. The total renal resistance fell from 72,608 to 27,125 dynes. sec. cm.$^{-5}$ with the primary decrease occurring in the afferent arteriolar segment.

Patient AC (Fig. 2), a 46-year-old Negro woman, was admitted to the hospital with moderate congestive heart failure and symptoms of headache, dizziness, and blurring of vision. She was believed to have combined rheumatic and hypertensive heart disease with mitral and aortic valvular regurgitation. Low-sodium house diet, digitalis preparations, and bed rest restored the cardiac compensation, and the blood pressure stabilized at 204 mm. Hg systolic and 131 mm. Hg diastolic.

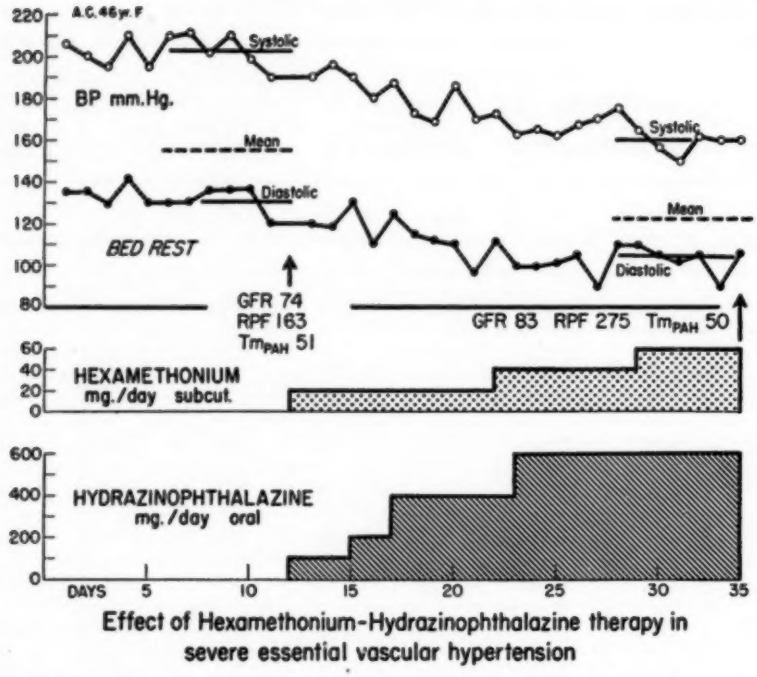

Fig. 2.—Clinical course of patient A.C., a 46-year-old Negro female with severe essential vascular hypertension.

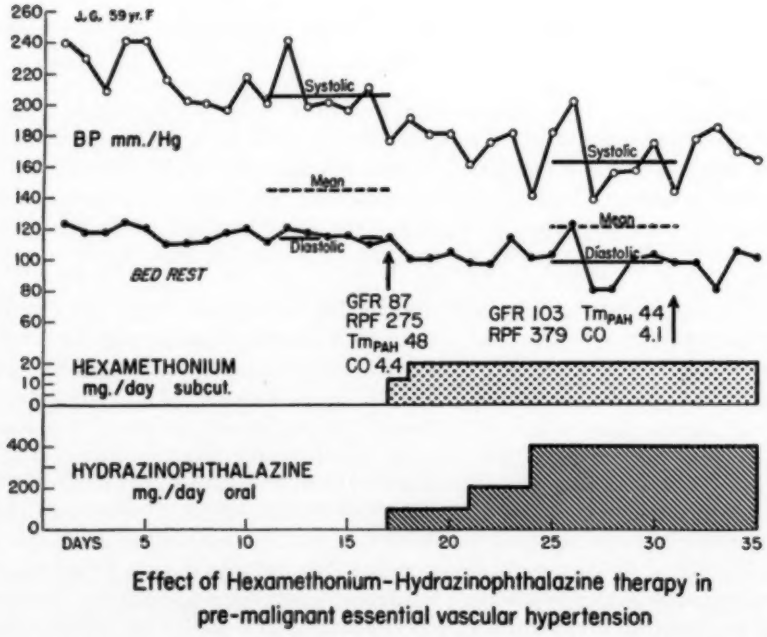

Fig. 3.—Clinical course of J.G., a 59-year-old female patient with premalignant essential vascular hypertension.

Drug therapy was begun on the twelfth hospital day. This resulted in a progressive decline in the blood pressure to a level of 165 mm. Hg systolic and 109 mm. Hg diastolic after three weeks of treatment. The renal plasma flow increased from 163 to 275 c.c. per minute. There was a slight increase in the glomerular filtration rate but no change in the maximal tubular capacity.

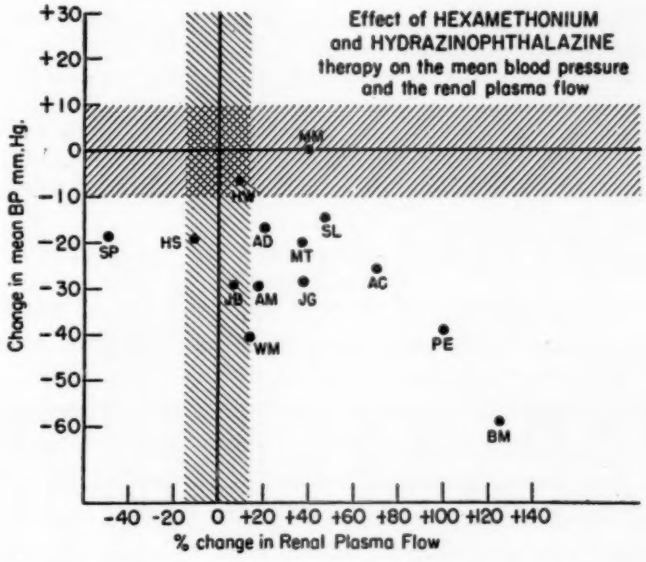

Fig. 4.—Effect of hexamethonium and hydrazinophthalazine therapy on the mean blood pressure and the renal plasma flow.

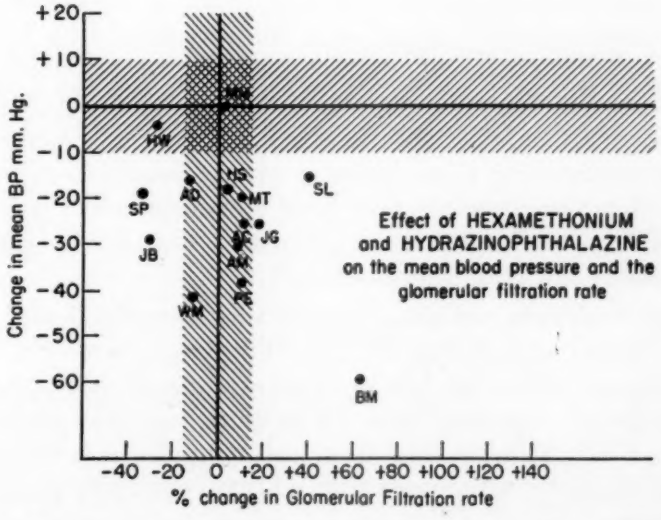

Fig. 5.—Effect of hexamethonium and hydrazinophthalazine on the mean blood pressure and the glomerular filtration rate.

The marked decrease in the afferent arteriolar resistance accounted for most of the decrease in total renal resistance, from 42,633 to 20,311 dynes.sec.cm.$^{-5}$. This patient was unable to cooperate fully on an outpatient basis and was lost from follow-up after a few months.

Patient JG (Fig. 3), a 59-year-old white female was admitted to the hospital with symptoms of congestive heart failure. She gave a history of known hypertension for ten years. The blood pressure on admission was 240 mm. Hg systolic and 130 mm. Hg diastolic. She was treated

initially with a regimen of bed rest, low-sodium house diet, and digitalis. The cardiac status improved without difficulty, and drug therapy was begun on the seventeenth hospital day. The response was excellent. The hypertensive retinopathy regressed from Grade 3 to Grade 2 severity. The blood pressure fell from an average of 206 mm. Hg systolic and 115 mm. Hg diastolic to 154 mm. Hg systolic and 97 mm. Hg diastolic after two weeks of treatment. The renal plasma flow increased from 275 to 379 c.c. per minute, and the glomerular filtration rate rose from 87 to 103 c.c. per minute. There was no significant change in the cardiac output or the maximal tubular capacity. The total renal resistance decreased 42 per cent, from 20,661 to 11,957 dynes.sec.cm.$^{-5}$. Again the greatest fall occurred in the afferent arteriolar segment. This patient has been maintained on an outpatient basis for two years with no recurrence of cardiac decompensation or progression of hypertensive disease. She has been able to resume her daily activities as a housewife.

DISCUSSION

The primary purpose of this study was to determine whether the increase in the renal blood flow could be demonstrated at the time of significant blood pressure fall following adequate oral hydrazinophthalazine therapy. This appeared to be a demonstrable finding in ten of the fourteen patients studied. Hexamethonium was used in low-dosage schedule merely to effect an accelerated response with hydrazinophthalazine as well as to counteract some of the side reactions of the drug. No attempt was made to attain a normotensive state with large doses of parenteral hexamethonium. That such measures with large doses of hexamethonium may lead to a significant decrease in renal blood flow and thus nullify the beneficial effect of hydrazinophthalazine can be postulated from case SP who received moderately large doses of hexamethonium (100 mg. per day) and demonstrated a 42 per cent fall in renal plasma flow. Cases HW and WM who received the next largest doses of hexamethonium (80 mg. per day) showed no increase in the renal blood flow in spite of the fact that one patient (WM) had a 40 mm. Hg fall in the mean blood pressure. Since the studies were carried out approximately three hours after the administration of the drugs, the high dose of hexamethonium may have been responsible for the decrease or the absence of increase in effective renal plasma flow, for it is known that this drug may decrease the flow transiently.[12-14]

There appeared to be a slight correlation between the degree of fall in blood pressure and the per cent change in the renal plasma flow (Fig. 4). However, there were cases in which the fall in blood pressure occurred without any improvement in the renal plasma flow. It is significant that patients SP and HS who showed a fall in renal plasma flow had a rapidly progressive hypertensive disease and died shortly afterwards from extensive necrotizing renal arteriolitis, proved at autopsy.

Improvement in renal plasma flow was demonstrable as late as 30 days after institution of therapy to suggest that tachyphylaxis did not occur. However, it has been mentioned that with prolonged therapy (over 6 months) the blood pressure and renal plasma flow revert to the control levels due to the development of drug tolerance.[15] It is possible that in certain patients progression of the disease may cause a decrease in renal plasma flow in spite of therapy. If this were actually true in all hypertensive patients, it would appear

that long-term hydrazinophthalazine would be ineffective in circumventing the relentless progression of renal and vascular deterioration. However, a more careful long-term follow-up in a greater number of cases would be desirable before a definite conclusion can be made on this point. The present study indicates that renal blood flow can be improved by oral hydrazinophthalazine, but no statement can be made as to the duration of this improvement. The failure of a single effective hypotensive dose to produce an increase in renal plasma flow after a period of continuous therapy reported by VanderKolk and associates[16] may have been due to the maximum effect produced on the kidneys by the maintenance therapy precluding a further rise with the single test dose.

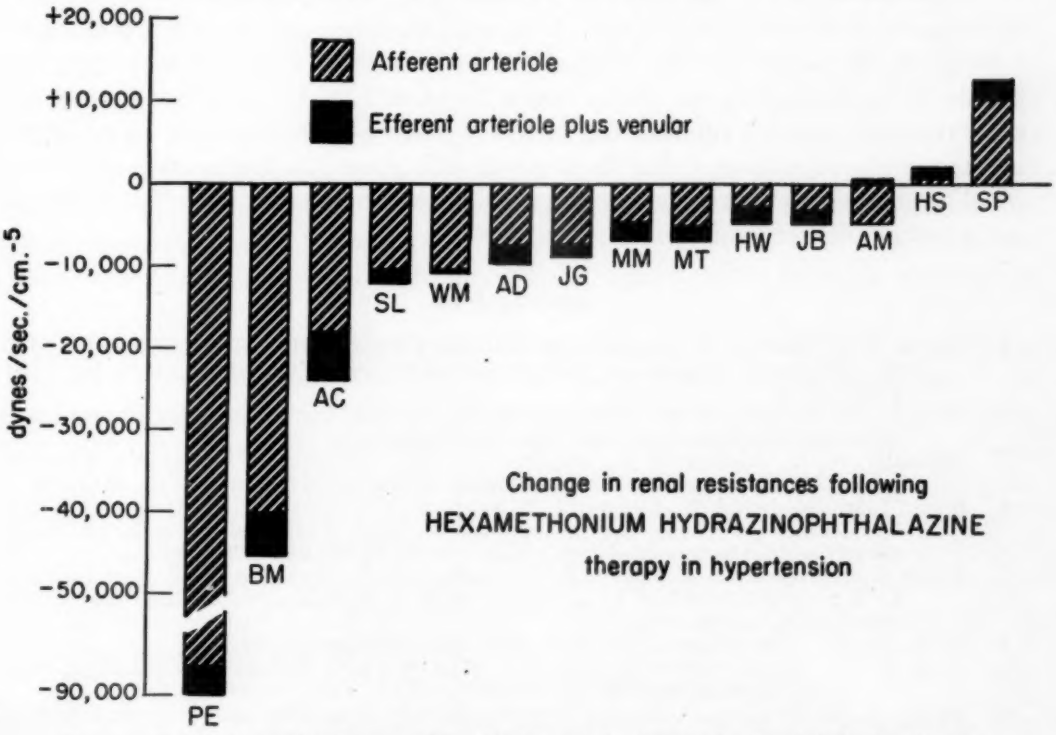

Fig. 6.—Change in renal resistances following hexamethonium-hydrazinophthalazine therapy in hypertension.

The improvement in renal blood flow without demonstrable changes in the tubular mass (Tm_{PAH}) indicated relative relief of renal ischemia characteristically found in late essential vascular hypertension. Apparently the notable decrease in afferent arteriolar resistance (Fig. 6) accounted for the increase in blood flow, although the slight concomitant decrease in efferent arteriolar resistance and fall in the mean pressure head prevented any consistent rise in the glomerular filtration rate (Fig. 5). It is of importance to note that improvement in renal blood flow could be attained without any significant increase in the cardiac output (Table II).

CONCLUSIONS

Controlled studies in fourteen severe hypertensive patients treated from two to six weeks with 400 to 600 mg. of oral hydrazinophthalazine per day and

with 20 to 100 mg. of subcutaneous hexamethonium per day in divided doses showed an effective fall of mean blood pressure in twelve patients and a significant increase in renal plasma flow in ten patients. Improvement in renal blood flow occurred without increase in cardiac output indicating a decrease in renal ischemia.

The authors are greatly indebted to Mrs. Leona deMarky, Mrs. Maxine Adams, and Mrs. Nancy Davenport for their nursing care and technical assistance in this study.

CONCLUSIONES IN INTERLINGUA

Esseva studiate le reactiones de 14 patientes con hypertension sever durante un curso de inter 2 e 6 septimanas de administrationes oral de 400 a 600 mg de hydrazinophthalazina per die combinate con injectiones subcutanee de 20 a 100 mg de hexamethonium per die in doses dividite. In 12 patientes un efficace reduction del pression median del sanguine esseva observate e in 10 patientes un augmento significative del fluxo renal del plasma. Melioration del fluxo renal de sanguine occurreva sin augmento del rendimento cardiac. Isto indicava un reduction del ischemia renal.

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ELECTROCARDIOGRAPHIC CHANGES DURING NOREPINEPHRINE-INDUCED HYPERTENSION IN NORMAL MAN

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THERE have been various reports on the effects of norepinephrine (noradrenalin; Arterenol)† in both man and animals, but to date there has been no systematic study of the electrocardiographic alterations occurring in normal man when the arterial blood pressure is acutely elevated and maintained at hypertensive levels with this drug. This communication presents the results of such a study.

Norepinephrine is a pressor amine which occurs normally in the human, and which is undoubtedly a mediator at the sympathetic nerve endings.[1] It has been found in high concentration in pheochromocytomas.[2,3] Its primary action is one of over-all peripheral vasoconstriction, the coronary arteries being a notable exception.[4,5] Coronary blood flow increases, either by direct vasodilatation, or secondary to stimulation of the myocardium.[6-11] Goldenberg and his colleagues[4] have administered norepinephrine to normal persons without adverse effects being noted. We have found no electrocardiographic changes during the treatment of shock of various etiologies with norepinephrine which could be attributed to this drug.[12,13]

Norepinephrine causes bradycardia in normal persons, a vagal effect secondary to elevation in the arterial blood pressure, and operating reflexogenically from the carotid sinus.[14]

METHOD

Nine clinically normal males were studied. All of them had been hospitalized for conditions unrelated to the cardiovascular system, and all had achieved complete clinical recovery at the time of this study. The ages of the patients ranged from 15 to 42 years, and all of the patients were highly cooperative. No patient was told to expect any side-reactions to the agents employed.

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Received for publication Feb. 28, 1955.

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†Norepinephrine was kindly supplied by the Winthrop-Stearns Co., Inc.

TABLE I

PATIENT	AGE (YR.)	CONTROLS BEFORE NOREPINEPHRINE			CHANGES WITH NOREPINEPHRINE			CHANGES AFTER ATROPINE SULFATE*		SIDE-REACTIONS
		BLOOD PRESSURE (MM. HG)	HEART RHYTHM	HEART RATE PER MIN.	MAXIMUM BLOOD PRESSURE (MM. HG)	HEART RHYTHM	SLOWEST VENTRICULAR RATE (AVERAGE) (BEATS/MIN.)	HEART RHYTHM	FASTEST VENTRICULAR RATE (BEATS/MIN.)	
AB	15	96/50	S.A.	81–88	152/90	Wandering pacemaker to the A-V node	50			Headache, rather severe
C	40	130/80	S.R.	94	190/100	S.B. & A.	52			Slight chest constriction and headache
A	20	104/60	S.A.	62–70	210/100	S.B.	42			None
B	17	110/70	S.B.	41	220/120	A-V dissociation	41			None
AZ	42	90/50	S.B.	52–58	170/110–180/90	A-V dissociation	36	A-V dissociation	55 (average)	Chest constriction, mild
ABC	39	120/80	S.A.	65–71	220/110	S.B.	59	S.A.	83	Palpitation; chest constriction
BB	42	106/60	S.R.	77	190/110	S.A. with premature nodal beats	42	S.R. with periods of premature nodal beats with fixed coupling	120 (average)	Cold sweating; headache
TO	29	108/50	S.A.	54–62	196/80	S.B. with premature nodal beats	41	Upper nodal rythm	58	"Throbbing in head"; chest constriction
BT	30	100/60	S.R.	62	190/100	S.B.	43			None

*1/150 grain subcutaneously.
S.A.—Sinus arrhythmia; S.R.—Sinus rhythm; S.B.—Sinus bradycardia.

Following the withdrawal of any medications for at least 24 hours prior to the onset of the study, the subject was made comfortable in a supine position, and an intravenous infusion containing 1.0 mg. of norepinephrine base in a 1,000 c.c. solution of 5 per cent dextrose in water was started at a very slow rate. The rate of flow was increased gradually until the arterial blood pressure was raised to significantly hypertensive levels, or until side-reactions prevented raising the blood pressure further.

Electrocardiograms were taken prior to the administration of norepinephrine, and at frequent intervals thereafter as the blood pressure was raised and again returned to normal. Records were obtained with either a Sanborn or Cambridge direct-writing electrocardiograph, and included the standard and aV limb leads, and chest leads V_{3R} through V_6. The "electrical position" of the heart in all cases studied was intermediate, semivertical, or vertical. No patients having semihorizontal or horizontal "electrical positions" were studied.

Four of the patients were given 1/150 grain of atropine sulfate subcutaneously when the arterial blood pressure had reached its peak—the aim being to block partially the vagal reflex secondary to the norepinephrine-induced hypertension. Larger dosages were not used because of the fear of producing dangerous side-effects (e.g., arrhythmias).

RESULTS

1. *Side Reactions.*—Side-reactions occurred in six patients, and were mild in five of them. Their presence sometimes was elicited only after direct questioning. Four patients noted symptoms only after atropine sulfate had been administered. No correlation was seen between the level of blood pressure obtained and the severity of symptoms. Table I lists the side-reactions which were reported.

2. *Arrhythmias.*—Various arrhythmias, all supraventricular in origin, occurred in five patients during norepinephrine infusion. In essence, the arrhythmias represented a dynamic competition between the sinus and A-V nodes for pacemaker function, and were undoubtedly secondary to the enhanced vagal tone and varying degrees of depression of the two nodes. The remaining four patients developed slowing of the heart rate with a persistent sinus mechanism during norepinephrine administration. The arrhythmias occurring with norepinephrine and after atropine sulfate are also listed in Table I.

3. *Electrocardiographic Contour Changes With Norepinephrine.*—The changes seen in the tracings taken at the peak of blood pressure elevation reflected the end stages of a consistent trend seen in serial tracings obtained as the blood pressure rose progressively in each patient. Accordingly, all the changes described below are comparisons of the control tracings with those obtained at the peak arterial blood pressure. T-wave changes in the right-sided precordial leads were usually the first significant electrocardiographic alteration observed as the blood pressure was raised. The relatively minor changes in P-wave amplitude were not analyzed.

QRS Complex: In eight of nine patients the R wave became taller in one or more of the left-sided precordial leads. In three patients, R became somewhat smaller in one of these leads, while becoming taller in another. In seven of nine patients, the S wave became somewhat deeper in one or more of the right-sided precordial leads. One patient (A.Z.) developed a deepening of S in V_3 and V_4 without any significant change in magnitude of R in V_5 or V_6.

S-T Segment: There was flattening of the S-T segment in Leads V_4 to V_6 in two patients (A and A.Z.). In patient A.Z., the S-T segment became depressed abnormally in Leads II and V_4.

T Wave: In every case the T wave became smaller, inverted, or more inverted in the right-sided precordial leads. In five patients, T became somewhat taller in the left-sided precordial leads, while in three patients it became smaller in these leads. Two of the latter patients were those showing significant S-T segment change, and in one of them the T wave became abnormally small (patient A). Comparable changes were sometimes seen in some of the extremity leads. In one record (patient A.B.) no significant T changes were seen in the left-sided precordial leads, but T became smaller in Leads II and aV_F, inverted in III, and taller in aV_L.

U Wave: In five of nine patients the U wave became visible or more marked in one or more of the right-sided chest leads.

4. *Electrocardiographic Contour Changes After Atropine While the Peak Arterial Blood Pressure Reached With Norepinephrine Was Maintained.*—Four patients were given atropine sulfate subcutaneously while the peak arterial blood pressure was maintained with norepinephrine. The electrocardiograms of two of these patients are shown in Figs. 1 and 2.

QRS Complex: In three of four patients, R became somewhat taller after atropine than it had been previously with norepinephrine alone in one or more of the left-sided precordial leads. In two patients, S became somewhat deeper in one or more of the right-sided chest leads. None of the changes in the QRS complex were striking.

S-T Segment: Depression of the S-T segment in Leads II, III, aV_F, V_4, and V_5 occurred in patient B.B. after the administration of atropine sulfate. The S-T segment in Lead V_5 of patient A.Z. showed depression after atropine sulfate.

T Wave: Patient A.Z. developed a diphasic T wave with initial negativity in Leads I, II, aV_F, V_4, and V_5, whereas the T waves had been completely upright in these leads both in the control tracing and the tracings taken during norepinephrine infusion alone. The T wave became less inverted in V_2, diphasic with initial positivity in V_3 (where previously upright), and showed no significant changes in V_{3R} and V_1. In patient A.B.C., the T waves became abnormally small in Leads I, and V_4 through V_6. After atropine sulfate, the amplitude of the T waves in patient B.B. decreased in Leads I, II, III, aV_R, aV_F, and V_3 through V_6, with initial negativity occurring in Leads III, aV_F, and V_4 through V_6. T became less inverted in V_{3R} and upright in V_1. In patient T.O., T became deeper in V_{3R}, V_1, and V_2, and taller in V_4.

DISCUSSION

We are unable to explain the electrocardiographic changes which occurred during norepinephrine-induced hypertension on any simple basis. Nor do the changes which occurred after atropine sulfate lend themselves to a simple explanation. Four of the nine patients studied developed abnormal S-T segment and/or T-wave changes in leads reflecting the left ventricle during norepinephrine-induced hypertension before or after atropine sulfate administration. Patients A and A.Z. showed abnormal changes with norepinephrine alone, whereas the abnormalities appeared in patients A.B.C. and B.B. only after the injection of atropine. Patient A.Z. also received atropine sulfate, and the electrocardiogram became more abnormal thereafter. In two of the patients (A.Z. and B.B.) the ST-T changes in some of the left-sided precordial leads are similar to those seen in left ventricular strain. A similar pattern is seen in an electrocardiogram obtained after the subcutaneous administration of norepinephrine and atropine sulfate which was reported by Littman and his coworkers.[15]

Certain inconsistencies in the data merit attention. An inconstant tendency for R to become taller in the left-sided chest leads and S to become deeper over the right precordium may be due to slight changes in the location of the transition zone in the horizontal plane. In the left-sided precordial leads, the T waves became taller, smaller, or showed no change. After atropine sulfate the T wave became smaller or diphasic in the left-sided precordial leads in three patients, and became taller or less inverted in one or more of the right precordial leads. These changes occurred irrespective of whether norepinephrine alone caused the T wave in the left-sided precordial leads to become taller or smaller. In the remaining patient given atropine sulfate (patient T.O.), the T wave became taller in the left precordial leads, and more inverted in the right-sided chest leads. At no time, however, did the S-T segment become more elevated in the left-sided chest leads, either with norepinephrine alone or after atropine.

The most consistent change noted with norepinephrine was for the T wave to become smaller, inverted, or more inverted in the right-sided chest leads. As noted above, this consistent trend was reversed in three of four patients after atropine sulfate.

There are various possible mechanisms by which norepinephrine-induced hypertension might cause the electrocardiographic changes noted: (1) Direct effects of norepinephrine on the myocardium, thereby directly affecting depolarization and/or repolarization, (2) effects of reflex vagal stimulation on the electrical activity of the heart, (3) alterations in configuration secondary to changes in heart rate, (4) changes due to altered position of the heart, (5) changes in depolarization and repolarization due to the induced systemic and pulmonary hypertension, (6) electrocardiographic changes secondary to emotional disturbance, due in turn to the side-effects of norepinephrine infusion and atropine sulfate administration. Each of these possibilities will be briefly discussed.

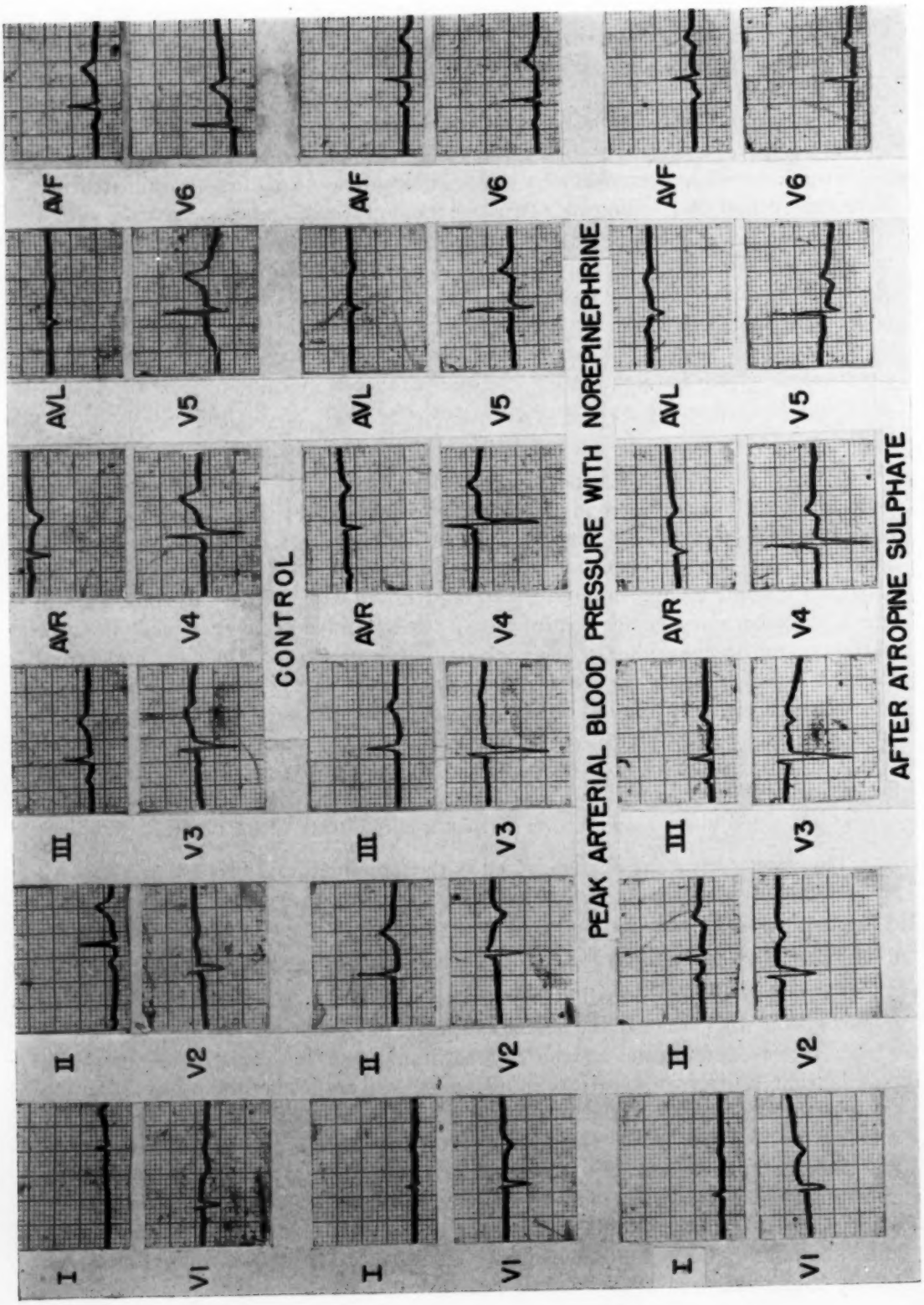

Fig. 1.—Patient A. Z. Discussed in text.

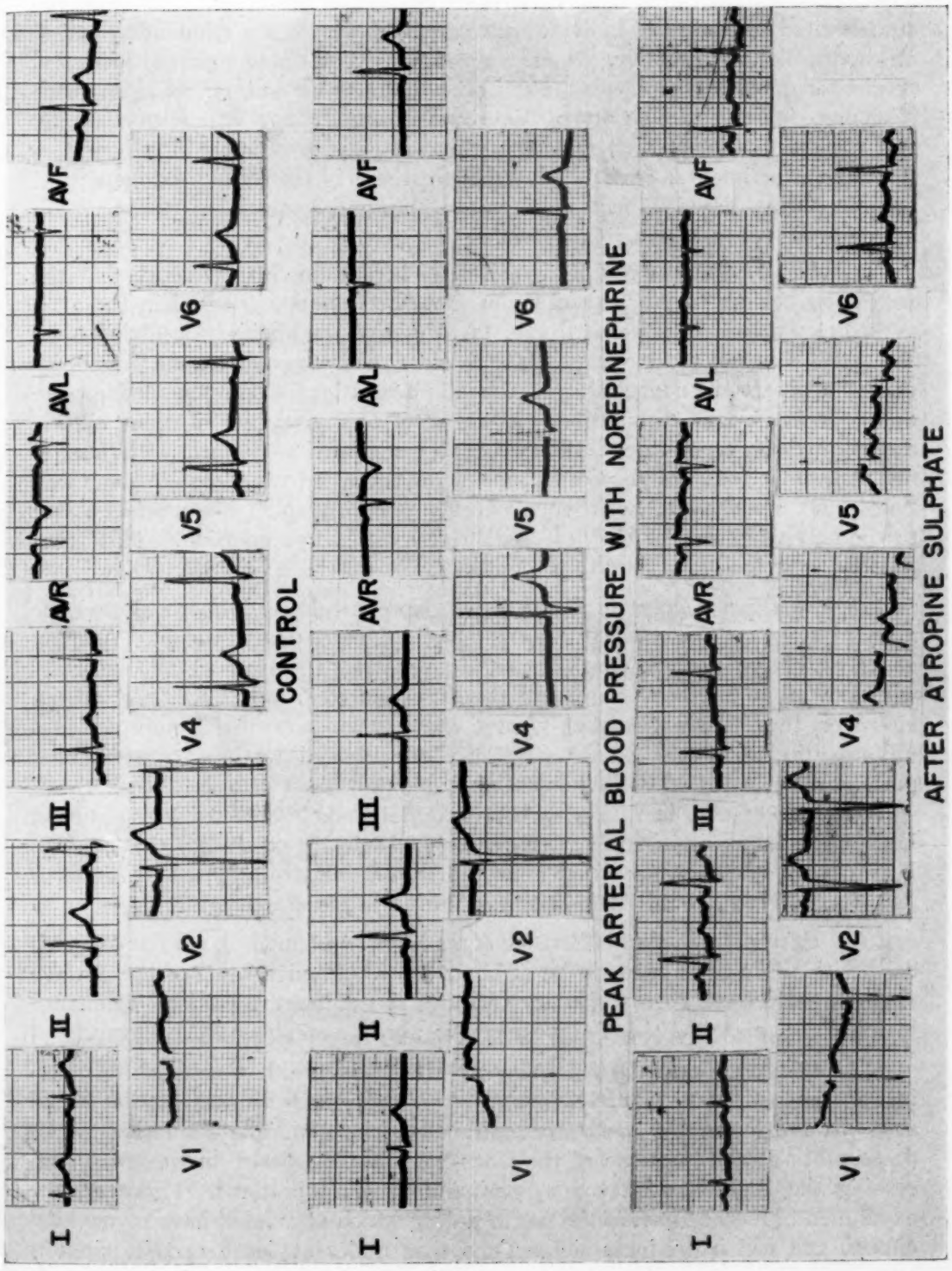

Fig. 2.—Patient B. B. Discussed in text.

(1) *Direct Effects of Norepinephrine on the Myocardium.*—Some of the studies cited previously[8,9] indicate that norepinephrine has a stimulating action on myocardial contractility. A more recent study on dogs[16] reported increased "heart force" with norepinephrine and other vasopressor amines. The influence of changes in heart rate on myocardial contractility is often difficult to evaluate, and the preparations which must be employed may themselves introduce considerable experimental error. Nevertheless, there is the strong evidence that norepinephrine directly affects the myocardium, and some of the electrocardiographic changes may be on this basis.

(2) *Vagal Effects on the Myocardium.*—There is no clear evidence that the vagi enter the ventricular myocardium, but acetylcholine released in the atria may directly influence the ventricle. Analysis of the changes occurring after the administration of atropine sulfate would appear to rule out the possibility that the observed changes during the administration of norepinephrine were due to reflex vagal stimulation. In three of four patients, atropine sulfate exaggerated or brought out changes that were previously seen with norepinephrine alone. It would seem as though the enhanced vagal tone in some way "protects" against the occurrence of electrocardiographic abnormalities due to the norepinephrine or the norepinephrine-induced hypertension. This "protection" may be due in part to the reflex slowing of the heart rate.

(3) *Effects of Change in Heart Rate.*—Norepinephrine infusion slowed the average heart rate significantly in eight of the nine patients studied. Ashman and Byer[17] have reported that the magnitude of the T wave generally increases with slowing of the heart rate, and this has been confirmed by us and others. However, the S-T segment and T-wave changes which occurred were not in a uniform direction, and hence can hardly be explained by heart rate changes alone. When atropine sulfate was given, and the heart rate increased, the T wave became smaller in the left-sided precordial leads in three of four patients, but became taller in one patient. We cannot rule out the possibility that changes in heart rate at times played an important role in determining the direction or magnitude of some of the changes observed in the electrocardiogram.

(4) *Effects of Changes in Position of the Heart.*—Changes in cardiac "electrical position" do not appear to be of importance. Though some of the T-wave changes could have been secondary to shifts in the heart "position" or change in its shape, many of the T-wave changes were unquestionably primary.

(5) *Effects of the Hypertension Itself.*—It is possible that some of the alterations seen represent "acute left heart strain." Even if true, our studies would shed little light on the mechanism of such a change. The similarity to the pattern of "strain" in some of the leads provokes the desire to speculate concerning the genesis of electrocardiographic "strain" patterns. However, the experimental method entails the use of a drug which may itself have myocardial effects, and which produces side-actions that under at least certain circumstances are known to alter the electrocardiogram (e.g., changes in heart rate).

Since it has been reported[4] that norepinephrine produces pulmonary as well as systemic hypertension, it might be that the most common change noted

in the electrocardiogram—algebraic reduction in T-wave amplitude in the right-sided chest leads—is due to acute strain on the right ventricle secondary to elevation in pulmonary artery pressure. This problem could be studied by the simultaneous recording of brachial artery pressure, pulmonary artery pressure, and the electrocardiogram during norepinephrine infusion, with careful observation on the time-sequence of changes as the systemic blood pressure was gradually elevated.

(6) *Effects of Emotional Disturbance Engendered by Side-reactions.*—Side-reactions were quite mild in five of the six patients in whom they were present. In four patients the side-reactions were reported only after atropine sulfate was given (that is, all patients given atropine reported side-reactions). It is possible that emotional reactions to the side-effects might have played a minor role in causing some of the electrocardiographic changes, but any major role would appear unlikely.

CONCLUSION

We can draw no specific conclusions concerning the genesis of the variable electrocardiographic changes, but it is our impression that the major factors to be considered are (1) the possible direct effects of norepinephrine on the ventricular myocardium, (2) heart rate changes, and (3) the effects of the acutely induced systemic and pulmonary hypertension. Any of the other factors discussed above may condition the electrocardiographic response. Further studies are planned to attempt to evaluate the relative importance of the various possible mechanisms mentioned.

Regardless of the mechanism involved, our results clearly indicate that norepinephrine infusion does produce significant electrocardiographic changes. Since norepinephrine secretion plays a part in conditions of stress, it may be one of the means by which some of the fluctuations in electrocardiographic pattern take place. This possibility should be considered whenever transient electrocardiographic contour changes are encountered.

SUMMARY

The electrocardiographic alterations occurring in normal males during norepinephrine-induced hypertension, before and after the administration of atropine sulfate, are reported. The possible mechanisms of the observed changes are discussed, but no specific conclusions can be reached. Further studies are indicated which may help to elucidate the mechanism of formation of the electrocardiographic "acute strain" pattern. It will be necessary to dissociate the direct myocardial effects of norepinephrine from its hypertensive action and from the marked reflex vagal stimulation which it produces.

Since norepinephrine probably plays a significant role under conditions of stress, our results indicate that fluctuations in the contour of the electrocardiogram may at times be explained by norepinephrine secretion.

SUMMARIO IN INTERLINGUA

Es reportate le alterationes electrocardiographic observate in masculos normal durante hypertension inducite per norepinephrina, ante e post le administration de sulfato atropinic. Le possibile mechanismos de iste alterationes es discutite, sed nulle conclusiones definitive pare deducibile. Studios additional es indicate pro elucidar le mechanismo del formation de configurationes electrocardiographic de "effortio acute." Il va esser necessari dissociar le directe effectos myocardiac de norepinephrina ab su action hypertensive e etiam ab le marcate stimulation del reflexo vagal que es producite per illo.

Proque norepinephrina ha probabilemente un rolo significative sub conditiones de stress, nostre resultatos indica que fluctuationes in le contorno del electrocardiogramma es a vices explicabile como effecto del secretion de norepinephrina.

We gratefully acknowledge the helpful suggestions of Dr. Louis N. Katz and Dr. Fred Pick during the course of this study.

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THE RELATION OF VALVE FUNCTION TO THE GENESIS OF THE SHARP FIRST SOUND IN MITRAL STENOSIS

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INTRODUCTION

OVER the years various explanations have been proposed as to the genesis of the first heart sound. Of these, the myogenic theory has developed from experiments demonstrating that heart sounds may be initiated by isolated strips of contracting myocardium and may be recorded even though valve action has been destroyed.[1-3] In contrast, it has been held that the first sound results from the striking, contacting force of the atrioventricular cusps and is independent of any myogenic factor. This viewpoint has been supported by Smith and his co-workers whose experiments with perfused dog hearts offer impressive evidence that the first heart sound is indeed the result of valve action alone.[4]

A third explanation relates the first sound to a combination of myogenic and valvular events and, additionally, to the vibrations that develop within the atrial chambers and the vascular tree.[5] The vibrations produced by each of these factors have been identified in the registrations of the stethoscopic microphone.[6] Those originating within the arteries and atria form the initial and terminal elements in these graphic recordings and produce low-frequency waves that are in the inaudible range. The vibrations produced by the closure of the atrioventricular valves form the mid-portion of the recordings and are high-frequency, clearly audible waves.

The question as to the precise mechanism for the genesis of the normal first sound extends, logically enough, to the explanation for abnormal first sounds.

Clinically the most significant variation from the normal is the "sharp" or short and high-pitched first sound that is heard most commonly in mitral stenosis. This abnormality often is confused with the "loud" sound that may be heard during a tachycardia, or in the presence of anemia or a febrile reaction, and that is characterized by an increase in intensity alone. The terms "sharp" and "loud" are specific expressions and when applied correctly identify first sounds that are fundamentally different. An area of confusion exists only because, in many instances, the sharp first sound may be loud, but this is not a constant or distinguishing feature.

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Received for publication March 3, 1955.

It has been customary to relate the variations in the duration, pitch, and intensity of the first sound to events which, from a theoretical viewpoint, alter the striking force of the atrioventricular leaflets. These are believed to include the structure of the valve and its musculotendinous support, the position of the leaflets at the time of ventricular systole, and the abruptness of ventricular contraction.

Thus far, in a small measure, certain of these factors have been correlated with the presence of a loud first sound. Levine has demonstrated that a loud sound is heard whenever the ventricles contract soon after the atrial contraction (P-R interval 0.04 to 0.12 sec.), and he reasons that this occurs because the atrioventricular leaflets are still low and relaxed in the ventricular cavity at the time of systole and snap upward with considerable striking force.[7] The explanation appears reasonable under the specifically stated circumstance of a short P-R interval. However, it is unlikely that this reasoning can explain the mechanism responsible for the sharp first sound unless one presumes that increased intra-atrial pressure or fibrosis of the musculotendinous supporting tissue holds the leaflets in a more dependent position at the time of ventricular systole. Such a concept fails to consider the movement of the cusps in mitral stenosis which is variously impaired because the downward arc of the leaflets is limited. Indeed, when fusion and fibrosis have been compounded by calcific deposits the valve actually may be relatively immobile. It is more logical to expect the explanation for the sharp first sound to be based on the restricted or altered movement of the leaflets rather than on their position or increased striking force. Finally, although a greater striking force may account for an increase in intensity, it does not explain a sound of shorter duration or higher pitch. An acceptable concept for the genesis of the sharp first sound must satisfy the basic laws governing its specific qualities and must be consistent with the actual mechanics of valve function.

The greatest burden in assaying the accuracy of any conclusion in this matter has been the inability to make critical observations within the contracting human heart. The advent of intracardiac surgery for mitral stenosis has offered an unusual opportunity for such investigation and has prompted this attempt to correlate the theory of sound production with the actual mechanism of valve function in order to define the fundamental issues which bring about a sharp first sound.

THE LAWS GOVERNING THE INTENSITY, PITCH, AND DURATION OF SOUND

As stated, the sharp first sound is characterized by its short duration and high pitch, and although the sound is usually considered loud, that is not one of its constant features. Loudness is a subjective term representing the degree of sensation and is dependent upon the intensity of sound and the sensitivity of the ear. It should be differentiated from intensity which refers to the amount of energy flowing in the sound waves without respect to the sensitivity of the receptor organ. However, both loudness and intensity are equally influenced by the distance from the origin of the sound, the amplitude of vibrations, the density

of the medium, and the area of the vibrating body. Loudness alone, distinct from intensity, is altered by pitch since the sensitivity of the ear increases in proportion to the pitch until the latter reaches a level of 1,000 vibrations per second, after which it decreases. The apparent loudness of the sharp first sound, then, may be related to its higher pitch.

Pitch is determined by the predominant frequency with which the source of sound vibrates and by the number of these vibrations which reach the ear per second. In a stringed instrument the pitch is inversely proportionate to the length of the string, directly proportionate to the square root of its tension, and inversely proportionate to the square root of its mass. This formula clarifies the role of the tension and area of the vibrating object. Obviously, the shorter, tighter, and lighter string produces the sound of higher pitch.

Theoretically, the heart more closely resembles a percussion rather than a stringed instrument with the valve leaflets acting as the taut vibrating membrane. The pitch of the sound produced by a percussion instrument is also governed by the tension and mass of the vibrating membrane and is not influenced by the force of the stimulus or variations in elasticity of the vibrating object.

These considerations related to pitch are incomplete without considering the structure of the mitral valve. It consists of a large anterior and smaller posterior cusp separated by two incisures in the anterolateral and posteromedial positions above the respective chordae tendineae. Since the incisures fall short of reaching the valve root or ring by several millimeters, a continuous rim of tissue is found at the periphery. The valve is supported by chordae tendineae which are more numerous along the free margin of the cusps and which assure a firm coaptation of the edges along the Y-shaped line of closure. In effect, then, one border of the valve is firmly clamped and the other is free, and at the time of closure the structure, from the point of view of acoustics, is a stretched two-dimensional membrane.

As indicated, the pitch or velocity of wave motion in a two-dimensional membrane is mathematically related to its tension, mass, and length, and, of these, tension is the most significant.

Duration is determined by the persistence of vibrations at their source which, in turn, is related to the inherent inertia of the vibrating object and to the length of time a stimulus is applied. Inherent inertia is a quality which is determined by the physical characteristics of the vibrating object and is unlikely to vary unless the latter is altered.

These theoretical factors related to the intensity, pitch, and duration of sound suggest that when the mitral valve functions as a stretched two-dimensional membrane, a first sound which is shorter in duration and higher in pitch than normal will develop when the inertia and the tension of the leaflets are increased, and when the length and mass of the cusps are decreased.

OBSERVATIONS

1. *The Mechanics of Valve Function.*—Although the examination of the mitral valve in the living patient is limited to those events that can be defined by the sense of touch, it is possible to evaluate the manner and degree in which the cusps are anchored, the mobility, tension, and flexibility of the leaflets, and the characteristics of the musculotendinous supporting structures during a commissurotomy for mitral stenosis, and to obtain the same information about the normal mitral valve during a commissurotomy for "pure" aortic stenosis.

It has been observed repeatedly that the normal leaflets are freely mobile and gradually float upward during diastole until they make contact at their free edges. With actual closure, the examiner can define a gentle bulging of the leaflets into the atrial cavity and this action, persisting until the leaflets are fully tensed, appears to be buffered by the restraining action of the elastic musculotendinous supporting structures. This intra-atrial displacement follows the physical contact of the free edges of the leaflets so closely that the entire action seems to represent one integrated movement. However, since the valve has already closed, the displacement is most likely an independent response to the rising pressure exerted by the column of blood contained within the ventricle.

These events are altered sharply by the presence of a significant stenosis. The cusps are anchored at the atrioventricular ring and, to a varying extent, along the fused commissures so that the leaflets, which no longer are freely mobile, move upward and make contact with decreased striking force. A further and more critical difference is recognizable for, with valve closure, the intra-atrial displacement begins and terminates most abruptly under great tension as if the buffering action of the musculotendinous supporting structure has been lost. The action may be likened to what occurs when a sail, rigged in its entire circumference by tight and inelastic lines, is caught by a full gust of wind.

In extreme cases extensive fibrosis or deposits of calcium convert the leaflets to firm, inflexible tissue. It is in this type of valve that palpation fails to disclose any ballooning into the atrium after closure, and in these instances, the valve ceases to act as a two-dimensional stretched membrane and functions acoustically as a rigidly clamped diaphragm.

2. *The Mechanics of Valve Function Related to the Presence of the Sharp First Sound.*—The total experience gained by examining the mitral valve points to the fact that two, closely allied movements take place at the time of closure: leaflet contact and intra-atrial displacement. Stenosis reduces the force of leaflet contact and either modifies or eliminates the intra-atrial displacement.

The altered mechanics of valve function in mitral stenosis have been correlated with the actual presence of a sharp first sound by recording, at the time of surgery, an analysis of the manner in which the valve closes, and by noting independently prior to operation an exact description of the auscultatory details.

It is a consistent fact that whenever a sharp first sound is heard, palpation of the leaflets reveals an abrupt ballooning effect. Furthermore, if surgery produces intra-atrial leaflet displacement in a valve in which it did not exist, a sharp first sound will develop when it had not been present previously. Finally a sharp

first sound will disappear as the result of commissurotomy only when the abnormal ballooning effect is replaced by a more gradual and buffered activity.

When extensive fibrosis or calcification of the leaflets or fusion and fixation of the musculotendinous supporting structures restrict the movement of the cusps, the valve functions as a diaphragm and intra-atrial displacement does not occur. In our experience a sharp first sound rarely is encountered under such circumstances. That a normal first sound is an unusual event in mitral stenosis, and that the diaphragm type of valve is a more common finding may be due to the fact that a sharp sound persists as long as some portion of the fixed cusps retains its ability to balloon into the atrial cavity during ventricular systole.

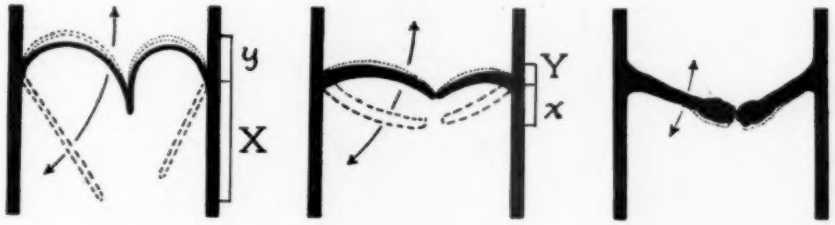


Fig. 1.—A schematic plan of the events in mitral valve closure under normal and pathologic conditions. *X*, represents the distance traversed by the valve leaflets. *y*, represents the intra-atrial displacement. *A* is a normal valve. *B* is a stenotic two-dimensional membrane with *x* representing the limited and restricted upward valve movement. *Y* is the abrupt intra-atrial displacement with balloonment. *C* is a heavily calcified valve which is like a stenotic diaphragm without ballooning effect.

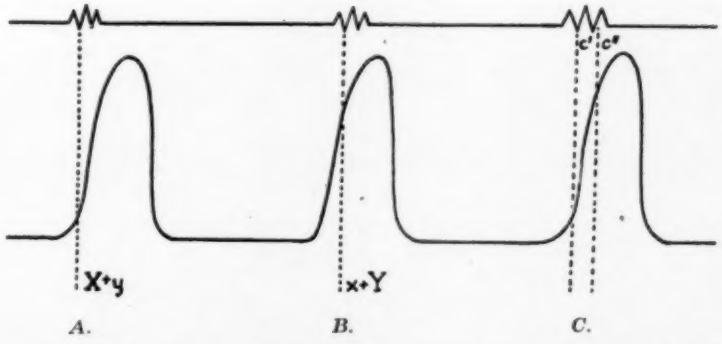


Fig. 2.—The predicted time relation of the first heart sound and the ventricular isometric period in normal and abnormal mitral valves. *A*, a normal valve where $X + y$ (see Fig. 1,*A*) represents the time required to produce the first sound during the early phase of isometric contraction in the ventricular pressure curve, approximately 0.013 sec. *B* is the valve described in Fig. 1,*B* where $x + Y$ is the time required to record the delayed first heart sound during the later phase of the isometric period, approximately 0.04 sec. *C* is the heavily calcified valve which is not mobile; c′, where absence of intra-atrial ballooning produces little or no delay in production of the first sound; c″, hypothetical timing of the first sound if the resistance of leaflets to closure was the main factor. This would result in marked delay of the first heart sound.

3. *The Mechanics of Valve Function Related to the Time of the First Heart Sound.*—Unless the first sound is analyzed by the cardiospectogram,[8] which for the present is an impractical routine, observations as to duration and pitch are based on subjective reactions. The mechanics of valve function likewise is

judged by a subjective sense that must be trained exquisitely before it is entirely reliable. Therefore, it is in the interest of accuracy to relate both of these findings to objectively determined data.

The closure of the normal mitral valve and the first sound, which is thereby produced, are known to take place in response to the early rise in ventricular pressure, (within 0.01 to 0.02 sec. after the cardiac impulse reaches the ventricular muscle). It is reasonable to expect that if the changes in valve function have been observed and recorded accurately they will reveal disruption of the normal time relation between the first sound and the ventricular isometric period.

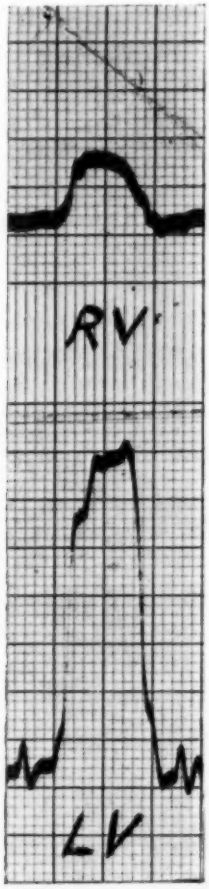


Fig. 3.—Simultaneous direct-chamber recordings of right (*RV*) and left (*LV*) ventricular pressure curves in a normal intact heart. This demonstrates that the isometric contraction period or phase occurs simultaneously in both ventricles.

Fig. 1,*A* is a schematic representation of the closure of the normal mitral valve. The time consumed by the upward movement of the leaflets, (*X*) the contact of the free edges, and the intra-atrial displacement (*y*) are such that the valvular component of the first heart sound occurs and is recorded during the early rise of ventricular pressure (Fig. 2,*A*). Otherwise stated, the first rise in ventricular pressure is sufficient to bring about leaflet contact, bulging, and the resultant first heart sound.

Fig. 1,*B* is a diagram of the closure of a stenotic valve in which the intra-atrial displacement is abrupt (*Y*). Palpation reveals that the force of the leaflet contact consistently is decreased which is the result of a limited and restricted upward movement (*x*). Since this action stems from a relative immobility of the cusps it is likely to require a greater intraventricular pressure before it is completed. When this effect is compounded by the increased resistance of

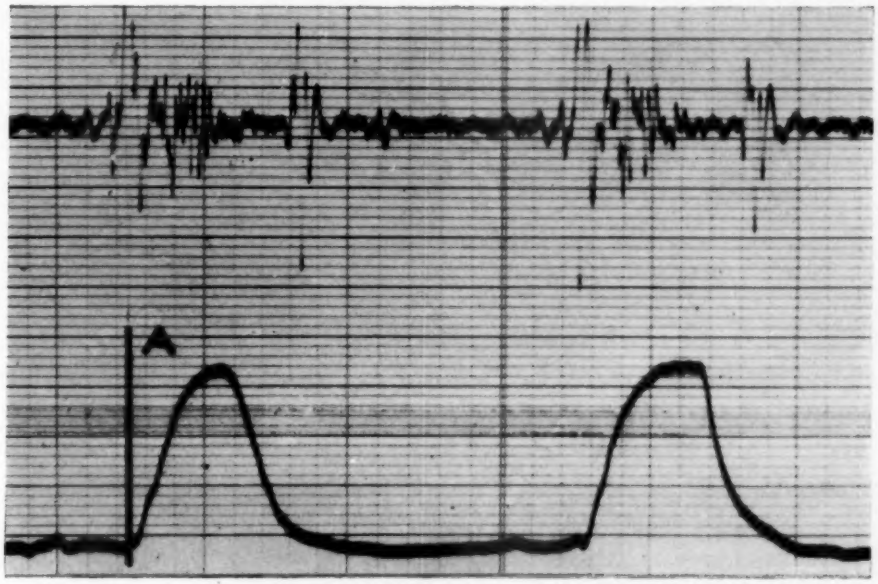


Fig. 4.

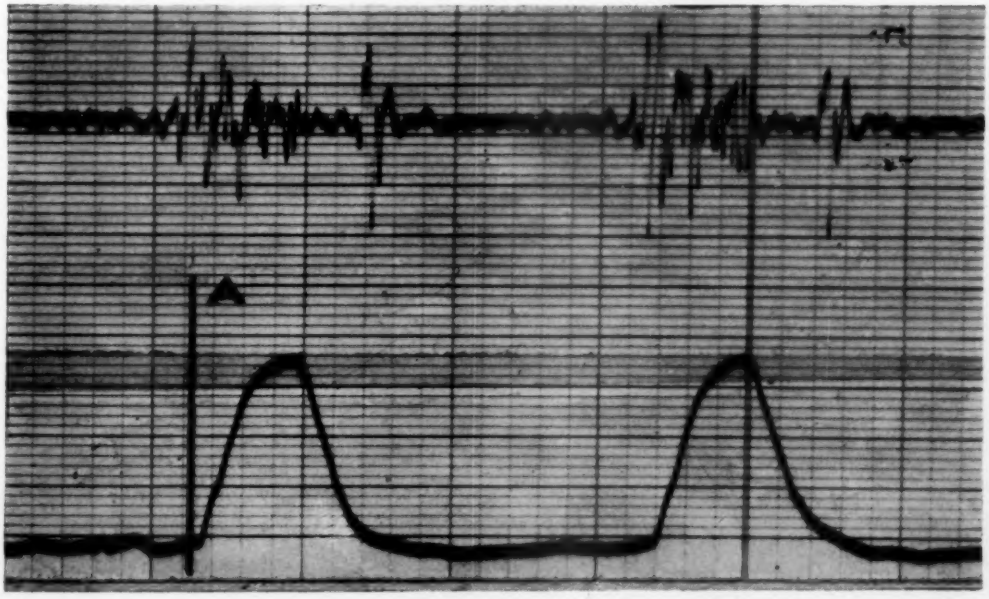


Fig. 5.

Figs. 4 and 5.—The position of the first sound in relation to the isometric period of the right ventricle (*A*) in the normal heart (cardiac catheterization).

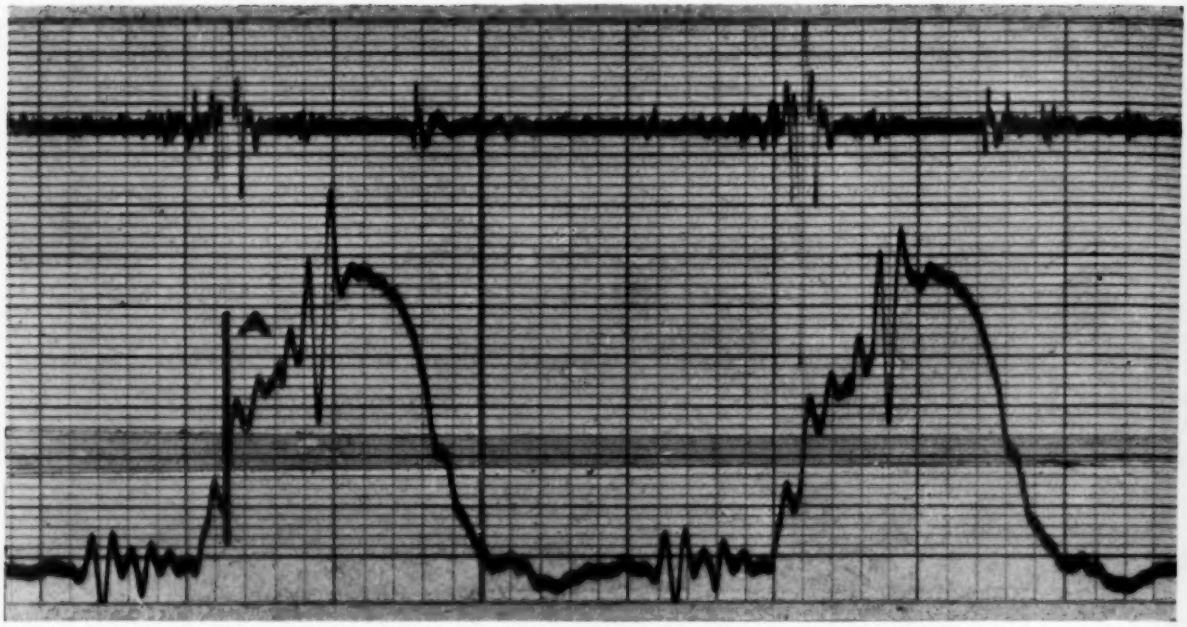


Fig. 6.

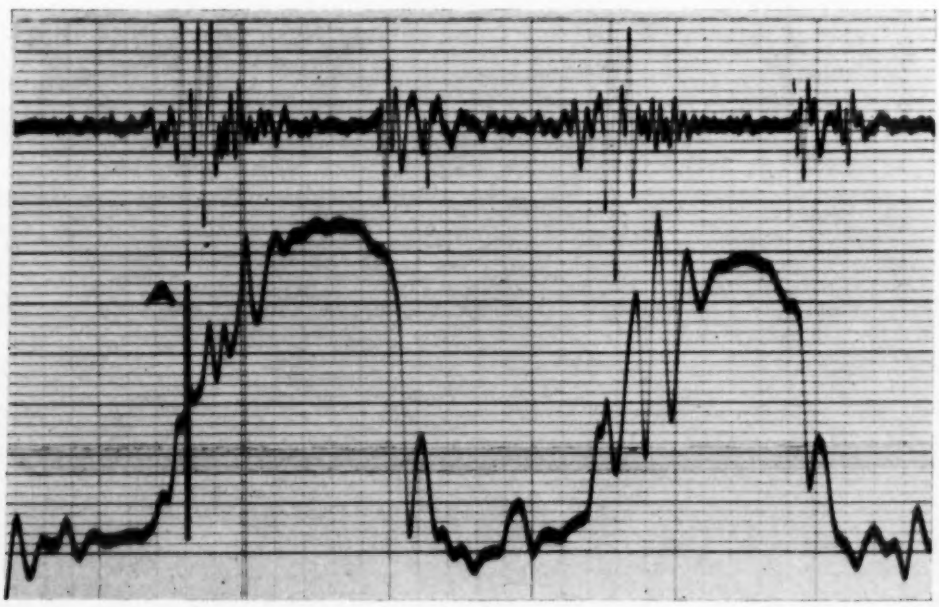


Fig. 7.

Figs. 6 and 7.—The delayed appearance of the first heart sound in relation to right ventricular pressures (*A*) in mitral stenosis (cardiac catheterization).

abrupt intra-atrial displacement, theoretically the first heart sound should be recorded during a later phase of the isometric period (Fig. 2,*B*).

Fig. 1,*C* depicts the closure of a calcified and fixed stenotic valve which does not balloon and functions acoustically like a diaphragm. If the delay in the

timing of the first sound is related to the increased resistance offered by the leaflets both to closure and intra-atrial displacement, then in this type of valve the absence of the ballooning detracts from the total effect and the delay should be less significant or it should not be present at all (Fig. 2,*c'*). If the timing is related only to the resistance of leaflets to closure, then the marked rigidity of this type of valve should produce a more exaggerated delay in the appearance of the first sound (Fig. 2,*c''*).

These possible relations have been explored clinically. Although in man a difference in timing may range from minus 50 to plus 30 milliseconds, the events in the right and left ventricles usually occur simultaneously (Fig. 3). Therefore,

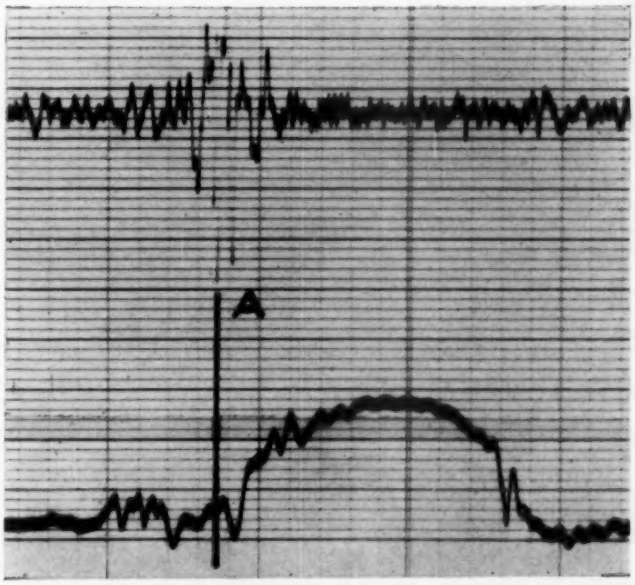
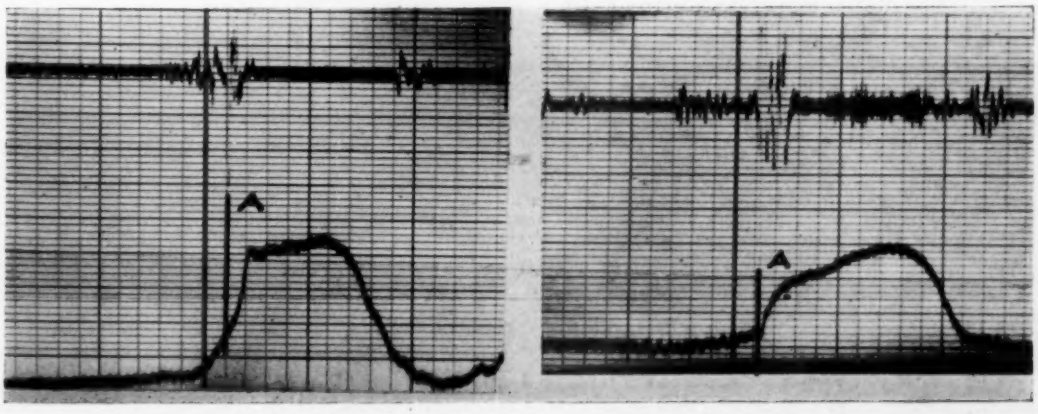


Fig. 8.—The normal position of the first heart sound in relation to right ventricular pressures (*A*) in a stenotic valve with calcified leaflets and no intra-atrial displacement (cardiac catheterization).

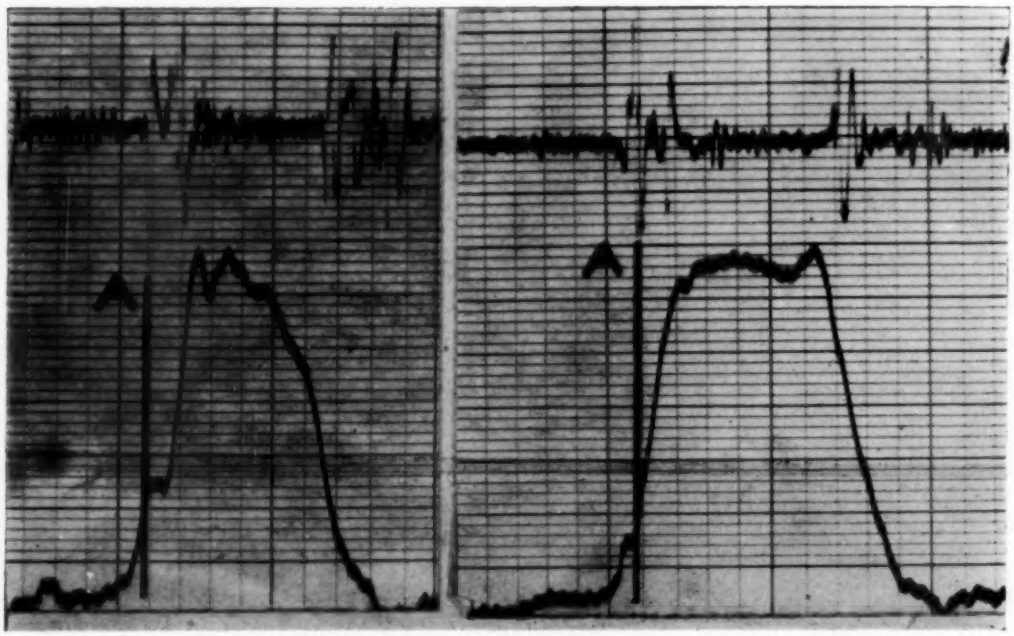


a. *b.*

Fig. 9.—*a*, The delayed appearance of the first heart sound (*A*) in mitral stenosis (direct left ventricular pressure). *b*, The normal position of the first heart sound (*A*) after commissurotomy (direct pressures).

the time relation of the first sound to the ventricular isometric period may be determined by recording sounds during right-heart catheterization. In the normal heart the onset of the valvular portion of the first sound occurs with the first rise in the right ventricular pressure (Figs. 4 and 5). The identical technique in patients with mitral stenosis reveals a normal or delayed first sound.

Figs. 6 and 7, which record a delay in timing, were obtained from two patients in whom the first sound was sharp, and the direct examination of the valve indicated the leaflets were displaced abruptly into the atrial cavity with each ventricular systole.



a. *b.*

Fig. 10.—*a*, The delayed appearance of the first heart sound (*A*) uncorrected by commissurotomy. *b*, (Direct pressure).

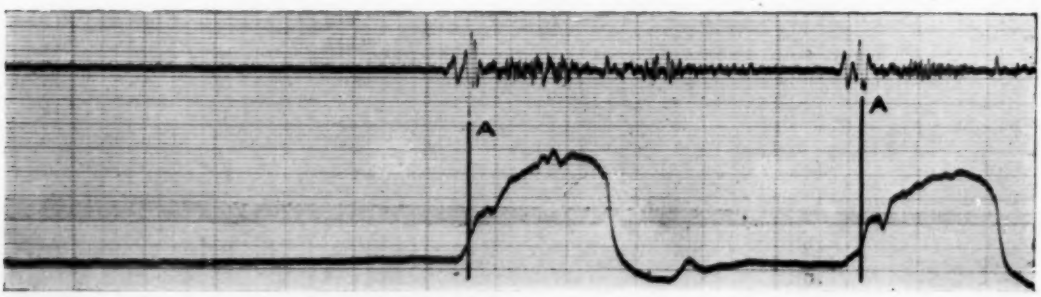


Fig. 11.—The failure of the length of diastole to influence the time of the first heart sound (*A*). Auricular fibrillation is present in this tracing.

Fig. 8, which records a normal time relation, was obtained from a patient with mitral stenosis in whom the first sound was normal, and the direct examination revealed the leaflets were rigid with extensive calcification and incapable of intra-atrial ballooning.

A direct technique which employs manometric readings from the left ventricle and sound recordings from the heart surface may be used at the time of surgery to demonstrate the time relation of the first sound to the isometric period.

Fig. 9,*a* was obtained with this technique and indicates a delay in timing in a patient in whom the first sound was sharp, and intra-atrial displacement was present. Fig. 9,*b* was obtained from the same subject immediately after a commissurotomy had reduced the abrupt intra-atrial ballooning to a more buffered distention of the leaflets and records a normal time relation of the sound to the rise in ventricular pressure. Subsequent examination disclosed a first sound which was normal in pitch and duration.

The direct technique was used in obtaining Fig. 10,*a* in a patient with mitral stenosis and a sharp first sound which illustrates a delay in the appearance of the first sound. Examination revealed the leaflets were elastic and free of calcium but anchored by unyielding and agglutinated chordae tendineae. This fixation was unaltered by commissurotomy and the delayed sharp first sound persisted (Fig. 10,*b*).

4. *The Length of Ventricular Diastole Related to the Timing of the First Sound.*—The question now arises as to the role exercised by the position of the leaflets at the time of systole and by the pressures developed within the ventricle in determining the time relation between the first sound and the isometric period. Conceivably the first sound could occur later in the isometric period if the leaflets are low in the ventricular cavity at the time of systole and traverse a greater distance before closure, or if the effective ventricular pressure is decreased.

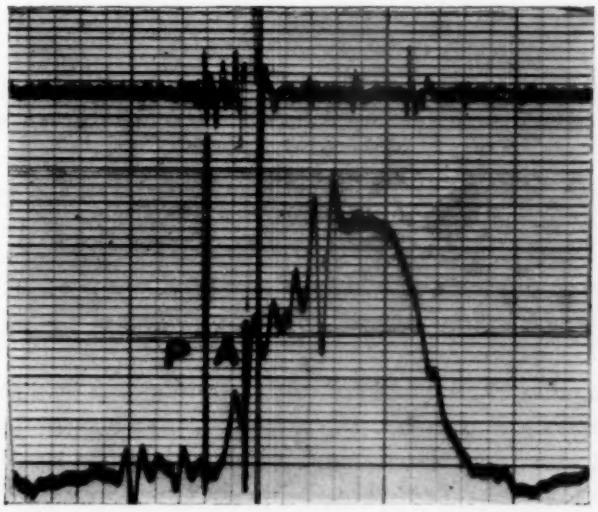


Fig. 12.—Delayed appearance of the first heart sound (*A*) with a presystolic accentuation of a mid-late disatolic murmur (*P-A*) occurring in the isometric phase of systole.

When atrial fibrillation is the dominant rhythm it is likely that the position of the leaflets at the time of systole varies with the length of the previous diastolic period. However, Fig. 11 illustrates a persistent and identical delay in the timing of the first sound even though the length of the diastolic period prior to each systole varies sharply. In addition the higher pressure developed in the

ventricle after the prolonged diastole does not alter the timing of the sound. In this patient on auscultation the first sound was sharp, and the direct examination of the valve revealed an abrupt intra-atrial displacement of the leaflets.

The same illustration (Fig. 11) indicates an increased amplitude of vibrations following the longer diastolic period. The variation in loudness which was discernible on auscultation did not obscure the fact that the first sound remained short and high-pitched. During the direct examination the force of the leaflet contact was noted to vary, and this presumably was responsible for the differences in the amplitude of the vibrations.

DISCUSSION

The study suggests that two events in the closure of the normal valve, the contracting force of the cusps and the intra-atrial displacement of the leaflets, are modified in mitral stenosis. The extent of the valvular deformity determines the alterations in mechanical function. It is the displacement of the leaflets alone, however, that is related to the production of the sharp first sound.

It is reasonable to expect that the scarring of the mitral cusps reduces the amount of leaflet tissue that bulges into the atrium during the ventricular isometric period. The resultant mechanical action is comparable to the events developing when a sail is tightly rigged and the area of canvas is reduced. Instead of responding to the force of a rising wind by filling gradually and bowing deeply, the sail tenses abruptly without a significant bulge. The factors responsible for this modification in the manner and extent of intra-atrial displacement also alter the basic characteristics of the cusps, as a source of sound for higher frequency vibrations, or a higher pitched sound, must be produced when the length and mass of a vibrating object are decreased.

The reduction in the length and mass of the cusps implies that the tissue is placed under greater tension at the time of valve closure. Logically, increased tension also could stem from a greater pressure exerted by the blood contained within the ventricle, or from the augmented restraining action of the musculotendinous supporting elements. The evidence at present strongly supports the view that the actual condition of the valve tissue is the most significant factor. However, on occasion the leaflets may be placed under great tension by the restrictive action of chordae tendineae which have become fibrotic and have lost their normal elasticity.

It is probable, also, that the fibroblastic proliferation in the leaflets accounts for the short duration of the sharp first sound. This pathologic process may alter the inherent inertia of the tissue, and thus decrease its ability to vibrate, although the change is not reflected in the mechanical function of the valve.

When intra-atrial displacement does not take place and the mitral valve functions as an acoustic diaphragm the pitch of the sound that is produced is no longer related to the length or tension, but to the elasticity, thickness, and radius of the tissue, and, of these, elasticity is the most important. Again it is likely that the extensive fibrosis and calcification or tissue changes in this type of valve reduce its elasticity to a minimum under which circumstance a lower pitched sound must result. These same changes should be expected to increase the inherent inertia of the tissue. Clinically, however, the sound produced by the

acoustic diaphragm is normal in duration. The explanation may rest with the fact that additional events govern the duration of sound produced by a diaphragm, or that calcified tissue, the most common structural finding in this circumstance, vibrates more readily than fibrotic tissue.

There remains for final consideration the delay in the appearance of the sharp first sound in relation to the isometric period. Since this time relation is encountered only in the presence of a ballooning effect, it must result from resistance offered by the leaflets to abrupt intra-atrial displacement which retards the completion of the final mechanical event necessary for the production of the first sound.

A possible error in terminology is revealed by the delay in appearance of the sharp first sound. If a mid-late diastolic murmur is prolonged until the onset of a delayed first sound (Fig. 12,*A*) it actually persists into the period of ventricular isometric contraction and therefore the latter portion of the murmur, usually termed presystolic, actually is systolic in time (Fig. 12,*P-A*).

From the clinical point of view although the sharp first sound is an important auscultatory finding in mitral stenosis, it is not related to the size of the mitral orifice, or to the physiologic severity of the lesion. Actually in the more advanced type of valvular involvement characterized by extensive calcification, it may be replaced by a sound which is normal in pitch and duration. Otherwise stated, a normal first sound is a late development in mitral stenosis and may be expected when the mechanical function of the valve is seriously and grossly impaired. It is at this time in the natural progress of dynamic stenosis that atrial fibrillation is most likely to develop obliterating the presystolic accentuation of the mid-late diastolic murmur. If the mid-portion of the diastolic murmur itself is faint, or difficult to recognize, because of a rapid cardiac rate, the diagnosis of mitral stenosis on the basis of auscultation alone cannot be concluded. Finally when these events are complicated by the presence of a systolic murmur at the apex, the diagnosis of predominant mitral insufficiency may be reached erroneously.

CONCLUSIONS

1. The theoretical factors related to the intensity, pitch, and duration of sound suggest that when the mitral valve functions as a stretched two-dimensional membrane a sharp first sound will develop when the inertia and tension of the leaflets are increased and when the length and mass are decreased.

2. Examination in the living patient reveals that two events in the closure of the normal valve, the contacting force of the cusps, and the intra-atrial displacement of the leaflets are modified in mitral stenosis.

3. The striking force of the free edges of the cusps is consistently decreased in mitral stenosis and is not related to the production of a sharp first sound.

4. Abrupt intra-atrial displacement of the leaflets is the only factor in mechanical function that is related to the production of a sharp first sound.

5. Abrupt intra-atrial displacement is the result of a decrease in the length and mass of valvular tissue and an increased leaflet tension which in turn accounts for the high pitch of the sharp first sound.

6. The fibroblastic proliferative change in the stenotic mitral valve increases

the inherent inertia of the tissue to vibrate and accounts for the short duration of the sharp first sound.

7. When extensive fibrosis or calcification converts the mitral valve to a diaphragm, intra-atrial displacement does not occur and the first sound is not sharp.

8. The first heart sound is delayed in relation to the ventricular isometric period when intra-atrial displacement is abrupt but is normal, independent of the rigidity of the valve, when the ballooning effect does not occur.

9. When the first sound is delayed, the presystolic accentuation of a mid-late diastolic murmur is actually systolic in time.

SUMMARIO IN INTERLINGUA

Le presente studio defini le genese del acute prime sono in stenosis mitral per correlationar le function mechanic del valvula deforme con le leges que determina le duration e altor del sono. Esseva registrate le evenimentos del clausura de normal e stenotic valvulas mitral in un gruppo de patientes de chirurgia cardiac. Le relation temporal del prime sono al periodo isometric ventricular esseva determinate per effectuar le registration de sonos simultaneemente con le determination del pression ventricular. Duo evenimentos in le clausura del valvula normal—le fortia de contacto del cuspides e le displaciamento intra-atrial del folios—esseva modificate in stenosis mitral. Le fortia de contacto esseva uniformemente reducite, e le displaciamento esseva plus abrupte o integremente eliminate.

Le prime sono esseva acute e retardate in relation al periodo isometric quando le ballonamento esseva abrupte. Iste typo de valvula functiona acusticamente como un tense membrana bidimensional, e nos concludeva que le acute e breve sono resultava a causa del reducite longitude e massa e del augmentate inertia e tension del folios. Le prime sono esseva normal in duration, altor, e tempo in casos in que un extense calcification del folios preveniva le displaciamento intra-atrial. Iste typo de valvula functiona acusticamente como un diaphragma in que le altor del sono es determinate exclusivemente per le grado de elasticitate.

Le investigationes justificava le conclusion que le typo e grado de displaciamento intra-atrial representa le evenimento mechanic del genese del sono acute e es un expression de cambiamentos que determina le qualitates vibratori del valvula.

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A STUDY OF THE ELECTROCARDIOGRAM AND VECTORCARDIOGRAM IN CONGENITAL HEART DISEASE

I. Electrocardiographic Criteria for Ventricular Hypertrophy

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INTRODUCTION

THE recognition and proper diagnosis of congenital heart disease are assuming progressively greater importance with the development of surgical corrective measures. There has, accordingly, been considerable recent interest in improving diagnostic laboratory methods. Cardiac catheterization and angiocardiography, while somewhat complex procedures, are of paramount importance in the differential diagnosis of these lesions. It is the purpose of this, and of subsequent communications, to evaluate the electrocardiogram and vectorcardiogram, relatively simple techniques, in the recognition and differential diagnosis of congenital cardiac malformations.

The accurate determination of ventricular hypertrophy and preponderance is the foremost task of the electrocardiogram in congenital heart disease. Certain congenital cardiac lesions produce essentially unilateral ventricular hypertrophy, and the electrocardiograms of patients with such malformations afforded the opportunity for studying electrocardiographic criteria of vertricular hypertrophy. After reviewing existing electrocardiographic criteria for ventricular hypertrophy it became apparent that wide differences exist. In an attempt to determine which are most valuable, we have taken several of these sets of criteria and have applied them to the patients in whom the type of ventricular hypertrophy present is known.

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Presented in part at The Second World Congress of Cardiology and the 27th Annual Scientific Session of the American Heart Association, Inc., Sept. 12-17, 1954, Washington, D. C.

Received for publication March 9, 1955.

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MATERIALS AND METHODS

We have selected for these studies 135 patients with congenital heart disease in whom the diagnosis appears to be well established and who have been observed by us for a period of 6 months to 10 years on the Pediatric and Medical Wards and in the Congenital Cardiac Clinic of The Mount Sinai Hospital. Seventy-five other patients who have been studied thoroughly by cardiac catheterization or angiocardiography, as well as by electrocardiograms and vectorcardiograms, have not been included because some doubt as to the exact diagnosis remains. The two patients with combined congenital and acquired heart disease were also excluded.

In nine patients the diagnosis was established at post-mortem examination, and in forty-one at the operating table. Ninety-two of the patients had cardiac catheterization performed, and fifty-seven were studied by means of angiocardiography. With the exception of ten patients with subaortic or aortic stenosis no cases were included unless at least one, and often several of the previously mentioned diagnostic methods had been applied. Of the twelve patients with congenital aortic or subaortic stenosis only two were studied by cardiac catheterization and angiocardiography. However, in all cases a Grade 4, or louder, systolic murmur was heard at the aortic area, was well transmitted along the carotids, and was accompanied by a thrill. All twelve patients showed significant left ventricular enlargement on fluoroscopy and x-ray examination, and had a carotid pulse tracing characteristic of this condition.

It is assumed that hypertrophy of a ventricle exists when a lesion is present which by virtue of its hemodynamics increases the work of that ventricle. Thus, patients with tetralogy of Fallot, pulmonic stenosis, interatrial septal defect, and aberrant insertion of pulmonic veins are considered to have right ventricular hypertrophy, while those with coarctation of the aorta, subaortic or aortic stenosis, and tricuspid atresia are considered to have left ventricular hypertrophy. Anatomic studies have proved the validity of these assumptions.[1-6] The electrocardiograms of the patients with other malformations (interventricular septal defect, patent ductus arteriosus, etc.) were excluded from the study of criteria of unilateral hypertrophy, since in these lesions an increased burden of work may fall on both ventricles. There were then sixty-six cases with right ventricular hypertrophy and twenty-eight with left ventricular hypertrophy, as defined previously. Table I shows the distribution by age and diagnosis of these ninety-four patients forming the basis of this report. It should be noted that only one patient in this group of ninety-four was below the age of three years. The electrocardiographic data of the remaining forty-one patients without clear unilateral ventricular hypertrophy will be presented in a subsequent report.

All electrocardiograms were recorded on a Technicon three-channel direct-writing cardiograph* at a paper speed of 50 or 100 mm./sec. and sometimes at the standard 25 mm./sec. as well, at one-half normal, normal, or one and one-half times normal standardization. In addition to the 12 conventional leads, Leads

*The frequency response of this instrument has been found to be flat to 70 cycles per second. The timing device has been found to be accurate.

V_{R7}, V_{R5}, and V_{R3}, as well as vector component Leads A, B, and C,[7] were frequently obtained. The simultaneous recording of three electrographic leads at increased paper speed and greater than normal standardization permitted greater accuracy of analysis. A spatial vectorcardiogram taken by the cube method of electrode placement[7] was obtained on each patient immediately after the electrocardiogram.

TABLE I. DISTRIBUTION OF CASES BY DIAGNOSIS AND AGE

DIAGNOSIS	AGE								
	UNDER 3 YR.	3-5 YR.	6-8 YR.	9-11 YR.	12-14 YR.	15-19 YR.	20-30 YR.	OVER 30 YR.	TOTAL
Right Ventricular Hypertrophy									
Tetralogy of Fallot		11	5	5	2	1	1	1	26
Pulmonic stenosis		1	6	3	3	4	1	2	20
Interatrial septal defect		3	2	3	1	3	3	4	19
Aberrant pulmonic vein	1								1
Total	1	15	13	11	6	8	5	7	66
Left Ventricular Hypertrophy									
Congenital aortic or subaortic stenosis		5	3		1	3			12
Coarctation of the aorta			1	2	1	5		2	11
Tricuspid atresia		3	1		1				5
Total		8	5	2	3	8		2	28

RESULTS

1. *Right Ventricular Hypertrophy.*—Goodwin's criteria for the electrocardiographic diagnosis of right ventricular hypertrophy in children[8] are: (1) V_1 R/S>1 and intrinsicoid deflection >0.03 sec., or (2) aV_R Q/R<1 or intrinsicoid deflection ≧ 0.06 sec. Forty-five of our sixty-six patients with right ventricular hypertrophy fell into the 3 to 14 year age group studied by Goodwin and 34 or 75 per cent* of them satisfied the criteria.

Table II lists Sokolow and Lyon's criteria for the electrocardiographic diagnosis of right ventricular hypertrophy.[9] These authors made the diagnosis of right ventricular hypertrophy when an electrocardiogram showed one or more of the characteristics listed. The frequency with which each criterion was positive in this series as well as in that of Sokolow and Lyon is also shown in Table II. In our series of sixty-six, all but one (Fig. 1) (98.5 per cent) of the electrocardiograms would be correctly diagnosed as right ventricular hypertrophy employing these criteria. The most frequent abnormalities were found in the voltage of R_{V1} and the ratio of R:S in V_1.

*In this, as well as subsequent reports comprising this study, per cents are given only as a guide and are not intended to transmit statistically evaluated data.

TABLE II. APPLICATION OF SOKOLOW AND LYON'S CRITERIA[9] FOR RIGHT VENTRICULAR HYPERTROPHY TO TWO SERIES OF PATIENTS WITH RIGHT VENTRICULAR HYPERTROPHY

CRITERIA FOR RIGHT VENTRICULAR HYPERTROPHY	SOKOLOW AND LYON'S SERIES—60 CASES		PRESENT SERIES 66 CASES	
	NO. OF CASES ABNORMAL	PER CENT OF CASES ABNORMAL	NO. OF CASES ABNORMAL	PER CENT OF CASES ABNORMAL
$R_{V_1} \geqq 7$ mm.	35	58	51	77
$S_{V_1} \leqq 2$ mm.	30	50	37	56
$S_{V_6} \leqq 7$ mm.	30	50	24	36
$R_{V_1} + S_{V_5} \geqq 10.5$ (above the age of 5 years)	26	72	34	72
$R_{V_5} \leqq 4$ mm.	21	35	15	23
$R/S\ V_5 \leqq 1$	19	32	24	36
$R_{aVR} \geqq 5$ mm.	18	30	12	18
$\frac{R/S\ V_5}{R/S\ V_1} \leqq .04$	15	25	5	8
$R/S\ V_1 > 4$ (under the age of 5 years)	9	38	52	79
$R/S\ V_1 > 1$ (above the age of 5 years)	8	22		
Ventricular activation time $V_1 \geqq .04$	42	70	41	62
T_{V_1} inverted with $R_{V_1} \geqq 5$ mm.	26	42	30	45
Any abnormal voltage	53	88	65	98

Table III shows the limits of normal voltage for certain deflections (maximum: R in V_1, V_{R_1}, and aV_R, and S in V_6; minimum: S in V_1 and R in V_6) in different age groups compiled by Kossmann[10] from several large series of cardiovascular normals.[11-20] Table III also indicates how frequently our fifty-one patients with right ventricular hypertrophy, but without an RSR′ pattern in V_1, exceeded these normal limits. Twenty-nine (57 per cent) of these fifty-one patients exhibited one or more deflections exceeding these limits. Twenty-six (51 per cent) of the fifty-one patients without an RSR′ pattern in V_1 had a preintrinsicoid deflection time in V_1 of 0.04 sec. or longer, a value greater than that of any normal.[9,10] Accepting one or more deviations from the normal range of voltage as described by Kossmann[10] or an increase in the preintrinsicoid deflection of V_1 (0.04 sec. or longer) as evidence of right ventricular hypertrophy, forty-one (80 per cent) of the electrocardiograms of this group of fifty-one patients with right ventricular hypertrophy without an RSR′ pattern in V_1 would be correctly interpreted as showing right ventricular hypertrophy.

Nine of the sixty-six patients with right ventricular hypertrophy were found to have the pattern of incomplete right bundle branch block as described by Wilson and associates[21] and Barker and Valencia,[22] characterized by an RSR′ pattern in V_1 with a QRS of 0.08 to 0.11 sec. duration. Three of these nine tracings revealed an R′ in V_1 with a voltage of 10 mm. or greater. One patient with a lesion producing right ventricular hypertrophy also had complete right bundle branch block, and his electrocardiogram revealed an R′ in V_1 of 12 mm. Five other patients with malformations resulting in right ventricular hypertrophy presented an RSR′ pattern in V_1 but their total QRS duration measured 0.07 sec. or less, and they were therefore not included in the incomplete right bundle branch block group.

TABLE III. APPLICATION OF NORMAL VOLTAGE RANGES* TO OUR FIFTY-ONE PATIENTS WITH RIGHT VENTRICULAR HYPERTROPHY

TABLE III. APPLICATION OF NORMAL VOLTAGE RANGES* TO OUR FIFTY-ONE PATIENTS WITH RIGHT VENTRICULAR HYPERTROPHY WITHOUT AN RSR′ OVER THE RIGHT PRECORDIUM

AGE (YR.)	NO. OF CASES	R_{V1}		S_{V1}		R_{V6}	
		MAXIMUM NORMAL VOLTAGE IN MM.	NO. OF PATIENTS WITH ABNORMAL R_{V1}	MINIMUM NORMAL VOLTAGE IN MM.	NO. OF PATIENTS WITH ABNORMAL S_{V1}	MINIMUM NORMAL VOLTAGE IN MM.	NO. OF PATIENTS WITH ABNORMAL R_{V6}
Under 1	1	29	0	0	0	0	0
1–10	26	20	7	0	0	5	6
10–20	17	16.7	3	0	0	3.5	2
20	7	15.5	1	.8	3	2.0	0
Total	51		11		3		8

AGE (YR.)	NO. OF CASES	S_{V6}		R_{aVR}		R_{V3R}	
		MAXIMUM NORMAL VOLTAGE IN MM.	NO. OF PATIENTS WITH ABNORMAL S_{V6}	MAXIMUM NORMAL VOLTAGE IN MM.	NO. OF PATIENTS WITH ABNORMAL R_{aVR}	MAXIMUM NORMAL VOLTAGE IN MM.	NO. OF PATIENTS WITH ABNORMAL R_{V3R}
Under 1	1	30	0	9	1		
1–10	26	13	2	19.5	0	9.9	10
10–20	17	11.3	4	8	2	8.0	7
20	7	14.3	1	3	3		
Total	51		7		6		17

*Compiled by Kossmann.[10]

TABLE IV. MEAN ELECTRIC AXIS OF QRS IN SIXTY-SIX PATIENTS WITH RIGHT VENTRICULAR HYPERTROPHY

ANGLE OF MEAN ELECTRIC AXIS	NO AXIS DEVIATION		RIGHT-AXIS DEVIATION		LEFT-AXIS DEVIATION			
	0° TO +45°	+45° TO +90°	+90° TO +135°	+135° TO +180°	0° TO −45°	−45° TO −90°	−90° TO −135°	−135° TO −180°
No. of patients	1	10	33	8	4	4	3	3
	17%		62%		21%			

Table IV shows an analysis of the octants and quadrants into which the electrical axes of the QRS of the sixty-six patients with right ventricular hypertrophy fell. Thus, in eleven (17 per cent) of the patients it fell between 0 and +90 degrees (no axis deviation), in forty-one (62 per cent) of the patients between +90 and +180 degrees (right-axis deviation), and in fourteen (21 per cent) between 0 and −180 degrees (left-axis deviation).[23,24]

TABLE V. APPLICATION OF SOME OF SOLOKOW AND LYON'S CRITERIA[25] FOR LEFT VENTRICULAR HYPERTROPHY TO TWENTY-EIGHT CASES OF CONGENITAL HEART DISEASE WITH LEFT VENTRICULAR HYPERTROPHY

CRITERIA FOR LEFT VENTRICULAR HYPERTROPHY	NO. OF CASES ABNORMAL
$R_1 + S_3 \geq 25$ mm.	5
R_{V5} or $V_6 \geq 26$ mm.	6
$R_{aVL} \geq 11$ mm.	3
$R_{V5} + S_{V1} \geq 35$ mm.	13
V_6 Ventricular Activation Time ≥ 0.06	2
S-T Segment Depression $\geq .5$ mm. in V_4, V_5, or V_6, or aV_L or aV_F	4
Number of patients with one or more of the above abnormal findings	15

2. *Left Ventricular Hypertrophy.*—Table V shows the frequency with which our cases with lesions producing left ventricular hypertrophy satisfied some of the specific voltage criteria of Sokolow and Lyon[25] for left ventricular hypertrophy. The electrocardiographic diagnosis of left ventricular hypert ophy could be made in fifteen out of twenty-eight of the cases (54 per cent) when these criteria were employed. Table VI lists the limits of normal compiled by Kossmann[10] for deflections which can be used in the electrocardiographic diagnosis of left ventricular hypertrophy. When employing these criteria, only nine (32 per cent) of the patients could be diagnosed as having left ventricular hypertrophy.

Table VII shows an analysis of the octants and quadrants into which the electrical axes of the QRS fell. In twenty (72 per cent) of the cases it fell between 0 and +90 degrees (no axis deviation), in two cases (7 per cent) between +90 and +180 degrees (right-axis deviation), and only in six (21 per cent) between 0 and −180 degrees (left-axis deviation).[23,24]

DISCUSSION

1. *Right Ventricular Hypertrophy.*—Goodwin studied the electrocardiogram in fifty-three normal subjects and in thirty-six patients with right ventricular hypertrophy, all between the ages of 3 and 14 years,[8] and established the electrocardiographic criteria described previously which were satisfied by 100 per cent of his cases. Our experience did not confirm this accuracy since eleven (25 per cent) of our forty-five patients with right ventricular hypertrophy in this age group (3-14 years) did not obey either of Goodwin's criteria.

Sokolow and Friedlander[12] analyzed the electrocardiograms of 163 normals, including thirteen infants. They established the limits of normal for the various voltages and the relationship between voltages. Sokolow and Lyon[9,25] observed

TABLE VI. APPLICATION OF NORMAL VOLTAGE RANGES TO OUR TWENTY-EIGHT PATIENTS WITH LEFT VENTRICULAR HYPERTROPHY

AGE (YR.)	NO. OF CASES	R_{V1}		R_{V6}		S_{V1}	
		MINIMUM NORMAL VOLTAGE IN MM.	NO. OF PATIENTS WITH ABNORMAL R_{V1}	MAXIMUM NORMAL VOLTAGE IN MM.	NO. OF PATIENTS WITH ABNORMAL R_{V6}	MAXIMUM NORMAL VOLTAGE IN MM.	NO. OF PATIENTS WITH ABNORMAL S_{V1}
1–10	14	.4	0	28.0	2	36.5	0
10–20	12	.4	1	25.0	4	26.6	2
20	2	0	0	22.6	1	26.2	0
Total	28		1		7		2

AGE	NO. OF CASES	S_{aVR}		R_{aVL}	
		MAXIMUM NORMAL VOLTAGE IN MM.	NO. OF PATIENTS WITH ABNORMAL S_{aVR}	MAXIMUM NORMAL VOLTAGE IN MM.	NO. OF PATIENTS WITH ABNORMAL R_{aVL}
1–10	14	19.5	1	11.8	0
10–20	12	17.0	0	10.1	3
20	2	11.0	0	10.1	0
Total	28		1		3

Minimum normal voltages for S_{V6} not listed since it is zero in all age groups.

TABLE VII. MEAN ELECTRIC AXIS OF QRS IN TWENTY-EIGHT PATIENTS WITH LEFT VENTRICULAR HYPERTROPHY

ANGLE OF MEAN ELECTRIC AXIS	NO AXIS DEVIATION		RIGHT-AXIS DEVIATION		LEFT-AXIS DEVIATION			
	0° TO +45°	+45° TO +90°	+90° TO +135°	+135° TO +180°	0° TO −45°	−45° TO −90°	−90° TO −135°	−135° TO −180°
No. of Patients	5	15	1	1	0	0	1	5

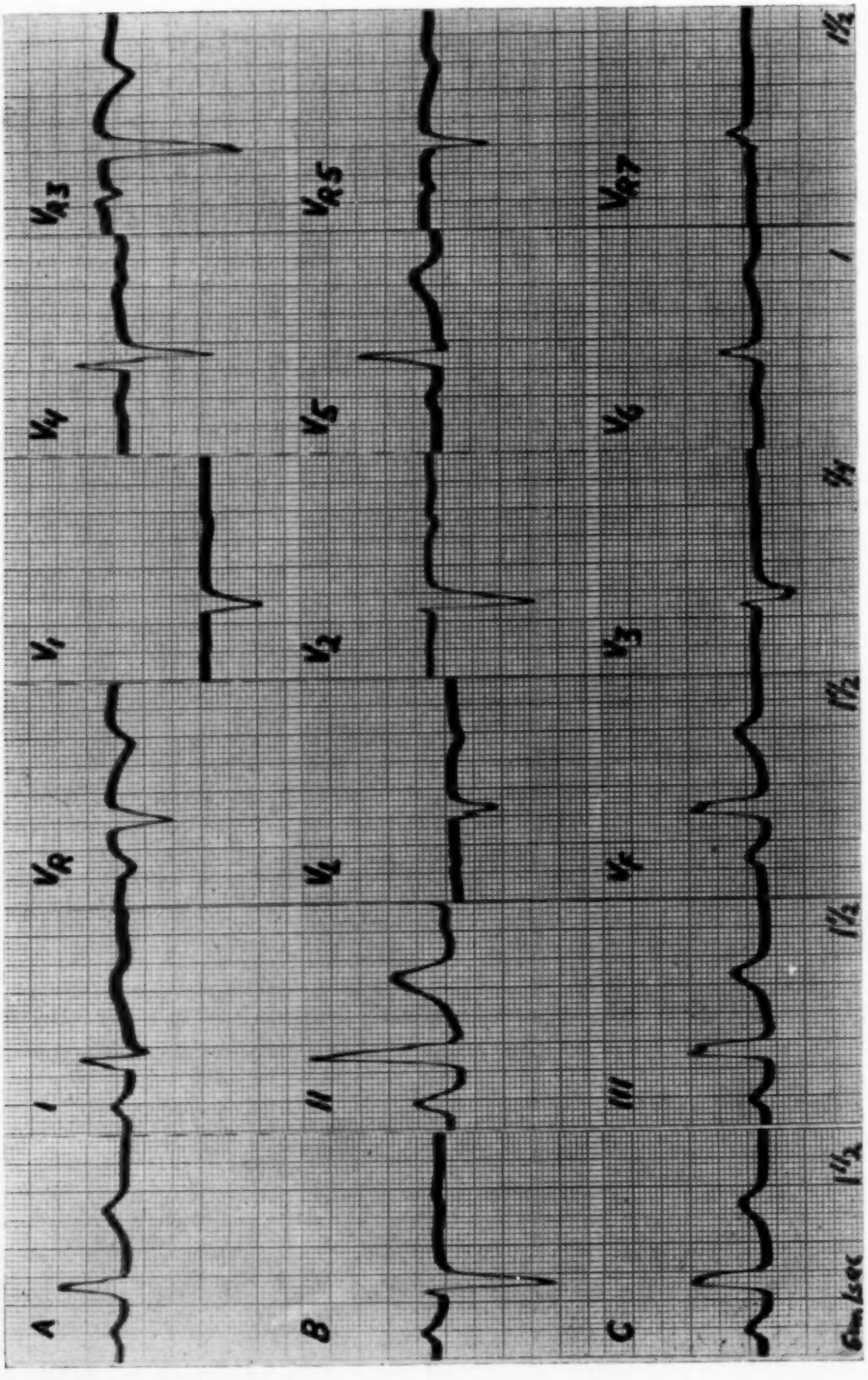

Fig. 1.—This electrocardiogram was obtained from an 8-year-old boy with tetralogy of Fallot, with the diagnosis confirmed at the time of surgery. This is interpreted as normal by all criteria studied. On all electrocardiograms paper speeds and standardizations are indicated at the bottom of the record.

the frequency with which these limits were exceeded by their cases with right and left ventricular hypertrophy. After applying Sokolow and Lyon's criteria for right ventricular hypertrophy[9] to our cases, the diagnosis could be made in all but one (98.5 per cent) of our patients (Fig. 1). The frequency with which each criterion was exceeded in our series agreed fairly well with the findings in their patients (Table II). However, by examining larger series of normals, especially the large series of infants and children studied by Ziegler,[20] it becomes apparent that the limits of normal established by Sokolow and Friedlander are too narrow, and that many of the normals in other series would be falsely diagnosed as having right ventricular hypertrophy by Sokolow and Lyon. The latter found the upper limit of normal voltage for the R wave in Lead V_1 to be 7 mm. In the 5-to-8-year age group, however, Ziegler found 27 per cent of forty-four normals had an R in V_1 greater than 7 mm.[20] All these cases would be incorrectly diagnosed as having right ventricular hypertrophy by Sokolow and Lyon. Since the electrocardiogram in normal infants and children frequently presents tall R deflections and small S deflections from the right precordium, many of these normals might satisfy Sokolow and Lyon's criteria for right ventricular hypertrophy.[9] It is in these younger age groups, particularly, that Sokolow and Lyon's criteria for the diagnosis of right ventricular hypertrophy are not strict enough.

We have applied more rigid limits to our electrocardiograms, thus establishing criteria which we believe to be more reliable. These criteria, however, are not applicable to all electrocardiograms. The presence of abnormalities such as conduction disturbances or myocardial infarction alters the electrocardiographic voltages, the ventricular activation time, or both, so that criteria employing these factors for establishing the electrocardiographic diagnosis of ventricular hypertrophy should not then be applied. In the presence of an RSR′ pattern in V_1 it may be impossible to determine whether or not a conduction defect exists. The RSR′ pattern in V_1 may represent (1) complete right bundle branch block, (2) incomplete right bundle branch block, (3) right ventricular hypertrophy, or (4) no abnormality.[25-27] The first category has been defined quite specifically,[21] but no certain way of distinguishing the last three categories by electrocardiographic means exists. We feel, therefore, that the criteria of right ventricular hypertrophy derived in the presence of normal conduction must not be applied to an electrocardiogram with an RSR′ pattern from the right precordium, since this pattern may represent the presence of a conduction disturbance. Attempts have been made to establish criteria for the diagnosis of right ventricular hypertrophy in the presence of complete and incomplete right bundle branch block. Barker and Valencia[22,28] have stated that when right ventricular hypertrophy and right bundle branch block coexist, a tall R′ deflection (usually greater than 10 mm. in incomplete right bundle branch block, and greater than 15 mm. in complete right bundle branch block) is noted in leads from the right side of the precordium. Only three of the nine patients with lesions producing right ventricular hypertrophy, whose electrocardiograms revealed incomplete right bundle branch block, had an R′ in V_1 with a voltage greater than 10 mm., and the single patient in this series with right ventricular

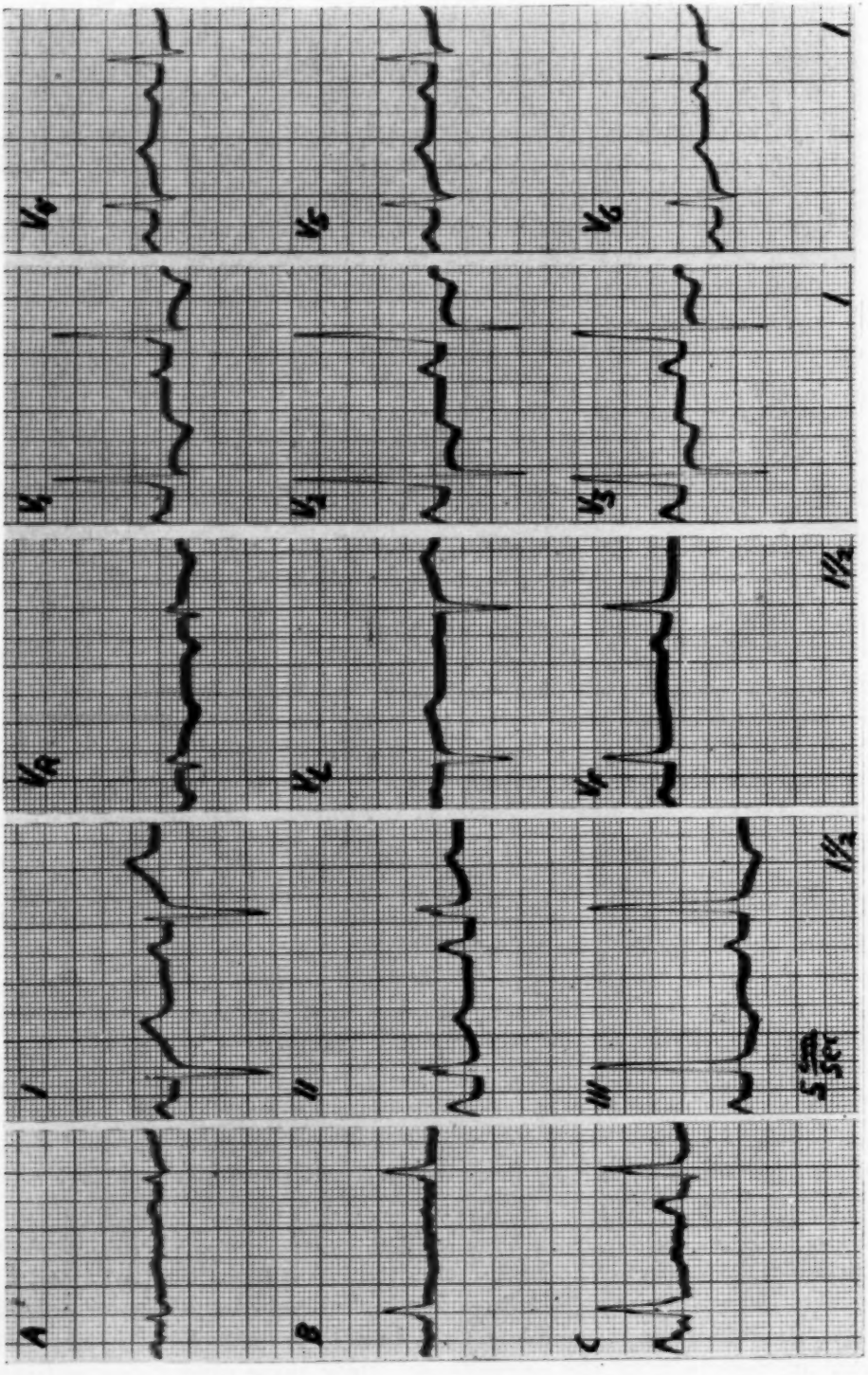

Fig. 2.—This electrocardiogram, of a 4-year-old girl with tetralogy of Fallot, demonstrates slurring of the upstroke of the R wave in Lead V_1, a finding in almost one-half of our patients with right ventricular hypertrophy. According to the criteria of Sokolow and Lyon, this tracing would be interpreted as showing right ventricular hypertrophy, and since the limits of normal voltage compiled by Kossmann are also exceeded, the stricter criteria for right ventricular hypertrophy defined in the text are similarly satisfied.

hypertrophy and complete right bundle branch block did not have an R′ in V_1 greater than 15 mm. We feel that at the present time the electrocardiogram cannot reliably solve the problem of the RSR′ pattern over the right precordium, but that in these cases, the spatial vectorcardiogram can provide the answer.[29,30]

The normal limits for the amplitude of deflections derived for the largest number of normal subjects (1,956), broken down by age groups available at this time, is the composite of several series published by Kossmann.[10] It appears to us, that in the absence of myocardial infarction or an RSR′ pattern in leads from the right side of the precordium, the presence of right ventricular hypertrophy can be accepted if an electrocardiogram exceeds one or more of the previously mentioned values for voltage or has an abnormally prolonged ventricular activation time over the right precordium. By employing these criteria, right ventricular hypertrophy was properly diagnosed in four-fifths of the patients who had lesions producing right ventricular hypertrophy, but who had no RSR′ pattern in V_1. We believe these to be the most satisfactory available criteria for the electrocardiographic diagnosis of right ventricular hypertrophy. An even larger percentage of patients with right ventricular hypertrophy could probably be diagnosed with reliability if the normal limits for the relationship between the various deflections (for example R/S V_{R3}, V_1, V_6, aV_R, etc.) were also available for a sufficiently large series of normal subjects.

The frequency with which the diagnosis was made with Sokolow and Lyon's criteria[9] in three series of patients with right ventricular hypertrophy (Meyers and associates,[31] Sokolow and Lyon[9] and our series), makes these useful as a screening test. Thus, if an electrocardiogram satisfies Sokolow and Lyon's criteria for right ventricular hypertrophy, as well as the stricter ones defined previously, we feel that right ventricular hypertrophy is virtually certain to be present (Fig. 2). When it does not satisfy either group of criteria, predominant right ventricular hypertrophy secondary to congenital heart disease is almost certainly ruled out. If, however, an electrocardiogram satisfies Sokolow and Lyon's criteria for right ventricular hypertrophy, but not the stricter criteria, it merely suggests the presence of right ventricular hypertrophy. In these cases, the electrocardiogram cannot give a definitive answer at the present time, and other tests such as the vectorcardiogram should be relied upon instead.

In the group of patients with lesions producing right ventricular hypertrophy, there was no significant difference in the severity of the disease, or the level of the right ventricular pressure in those patients with normal electrocardiograms, those with electrocardiograms showing right ventricular hypertrophy as defined by the stricter criteria outlined previously, and those with an RSR′ pattern in V_1. There was, however, a distinctly higher incidence of the RSR′ pattern in patients with interatrial septal defect. These findings are in essential agreement with those of other observers[32] who have noted the presence of normal electrocardiograms in some cases of congenital heart disease with right ventricular hypertension. Cosby and associates,[33] however, found that there were normal electrocardiograms only in those patients with congenital heart disease who had the lowest pressure and work levels. No correlation

could be established in our series between the amplitude of any single deflection and the level of right ventricular pressure. Other observers[32,34] similarly found no correlation between right ventricular pressure and/or work and the amplitude of any electrocardiographic deflections. Meyers and associates found no distinct correlation between cardiac weight, ventricular ratio, or thickness of ventricular wall with the electrocardiographic pattern.[31]

It has been noted that the occurrence of the incomplete right bundle branch block pattern as opposed to the right ventricular hypertrophy pattern is not related to the pressure or work level of the right ventricle.[33,35,36] It is our belief, on the basis of vectorcardiographic observations in this laboratory,[29,30] that in the great majority of patients with right ventricular hypertrophy the electrocardiographic pattern that has been named incomplete right bundle branch block actually indicates right ventricular hypertrophy and does not reflect a conduction disturbance at all. The spatial vectorcardiogram is necessary, however, to clarify each particular case (Fig. 3).

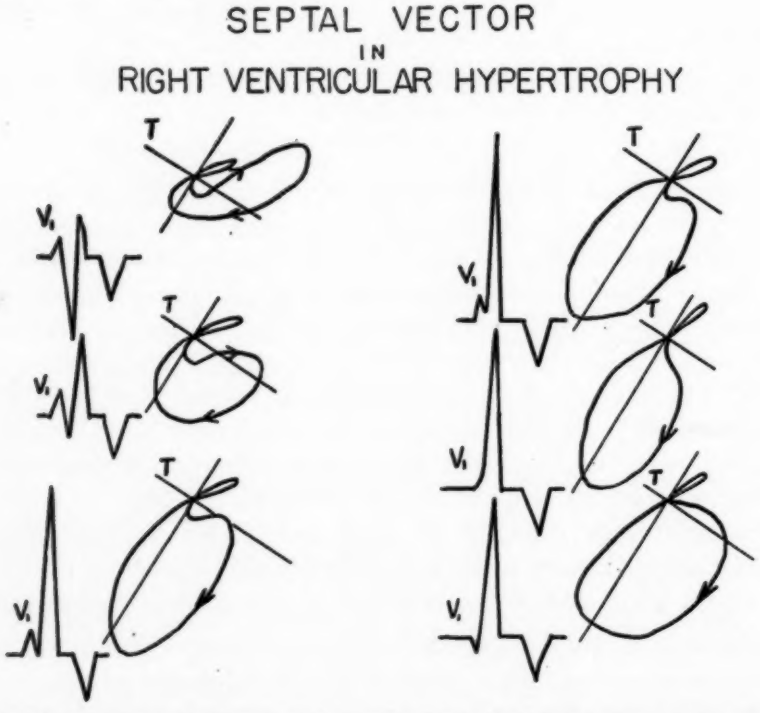

Fig. 3.—This illustrates the sequence of contours of the horizontal plane vectorcardiograms that we have encountered in patients with right ventricular hypertrophy, and the corresponding electrocardiographic Lead V_1. The various electrocardiographic configurations are due merely to variations of the fundamental right ventricular hypertrophy vector pattern.

Almost one-half of the patients with right ventricular hypertrophy revealed a slurred upstroke of R_{V1} (Fig. 2). The relative frequency of this finding in this series is in part related to the rapid paper speed at which the tracings were taken. Although this finding is not entirely specific and has rarely been seen in our laboratory in normal infants, it is highly suggestive of right ventricular hypertrophy when present. This finding in right ventricular hypertrophy

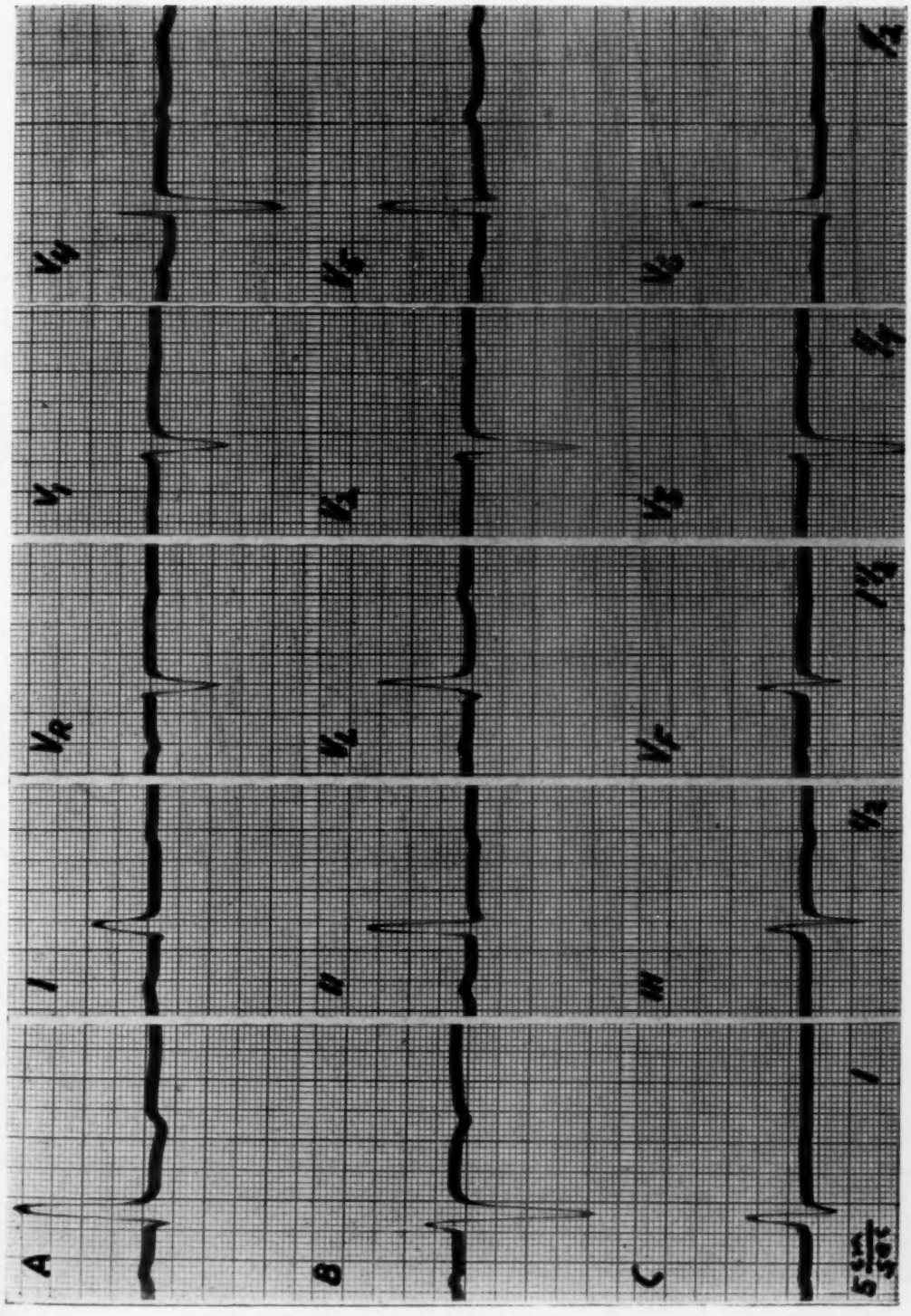

Fig. 4.—This electrocardiogram is from a 10-year-old boy with coarctation of the aorta and associated subaortic stenosis. This tracing would be interpreted as revealing left ventricular hypertrophy by the criteria of Sokolow and Lyon, and exceeds the limits of normal compiled by Kossmann, thus satisfying the stricter criteria for left ventricular hypertrophy defined in the text as well. Note that Leads V_1 to V_2 were taken at one-fourth normal, and V_4 to V_6 at one-half normal standardization.

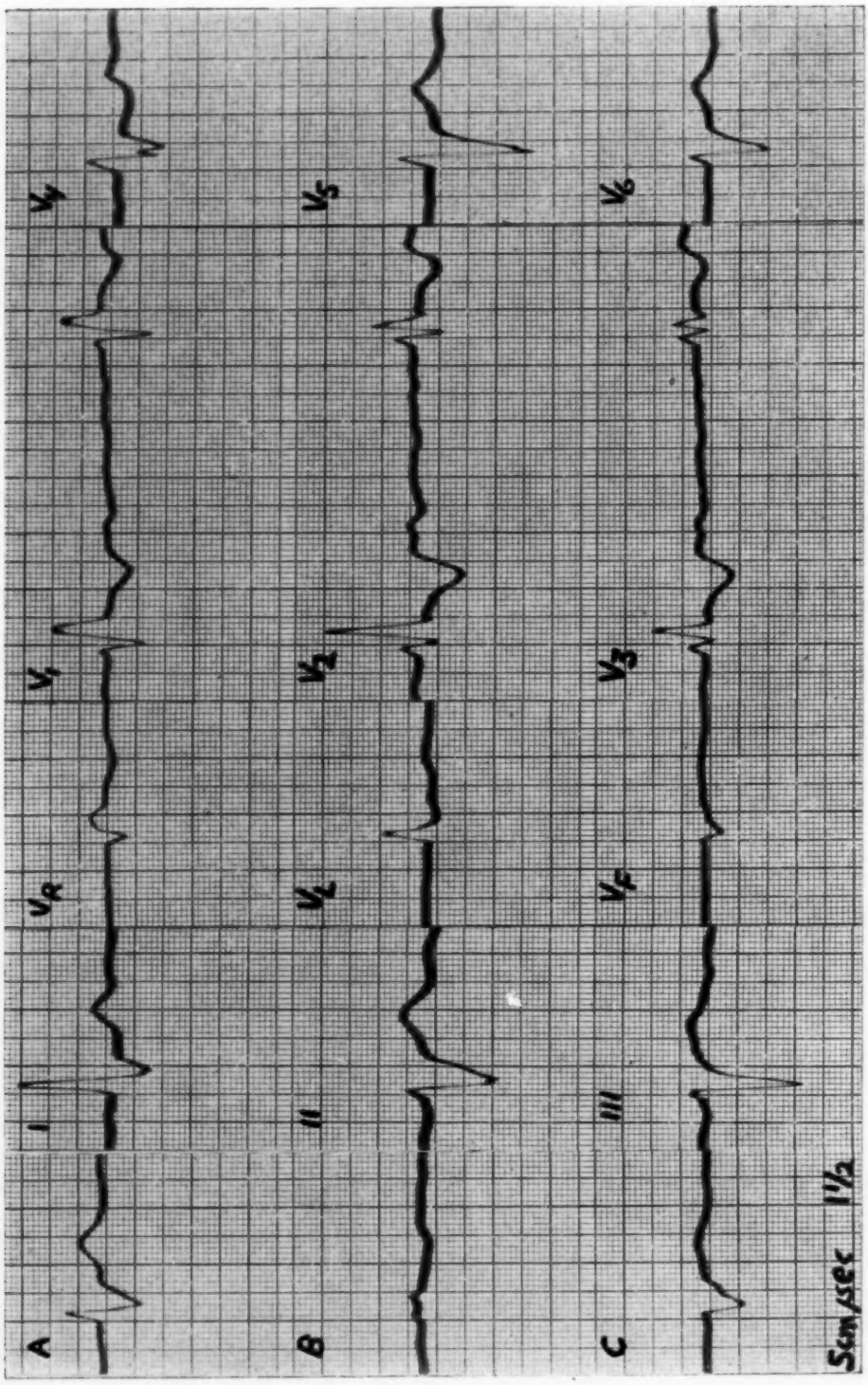

Fig. 5.—This electrocardiogram from a 35-year-old female with interatrial septal defect demonstrates the association of left-axis deviation and right bundle branch block in a patient with a lesion producing right ventricular hypertrophy.

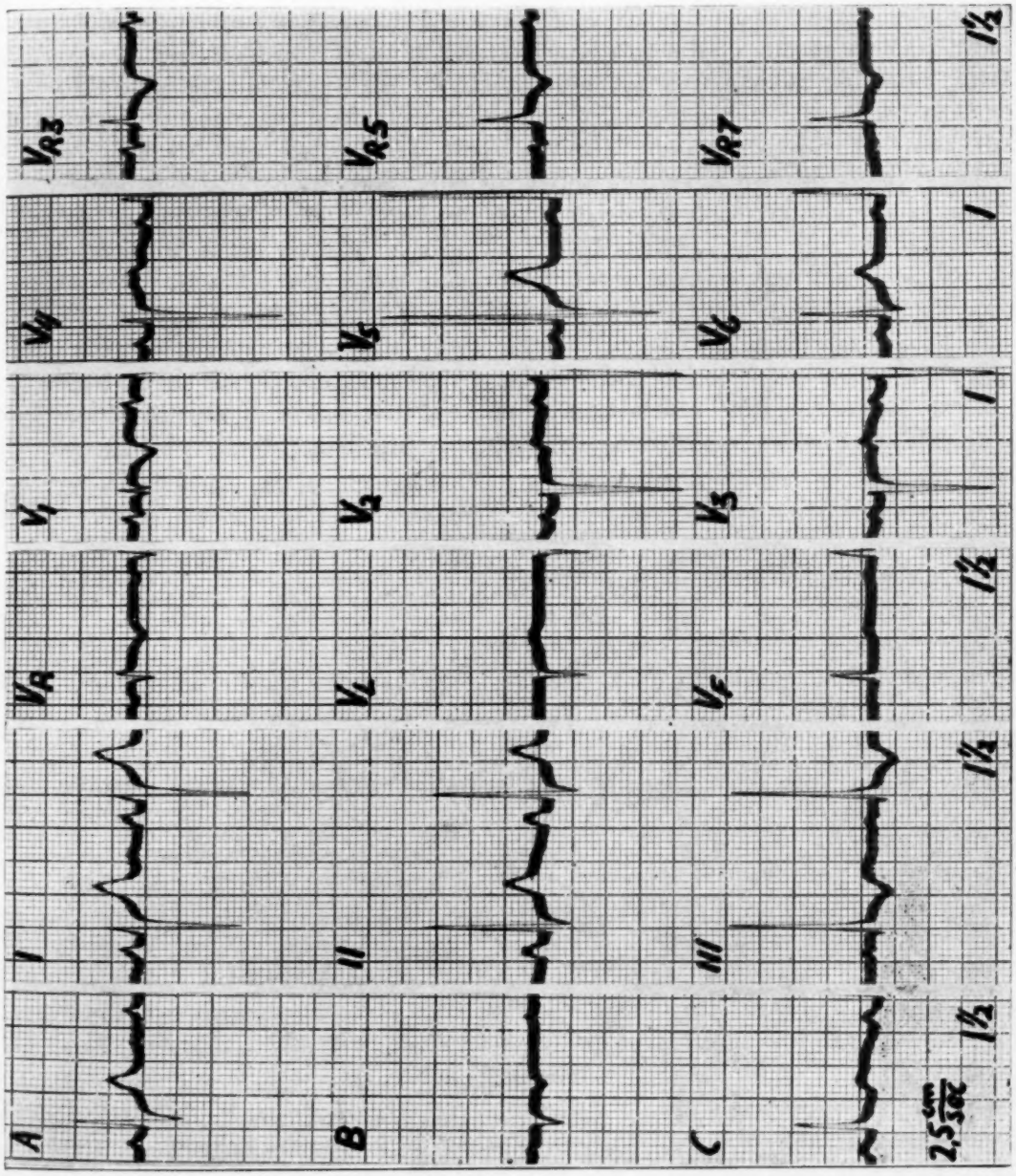

Fig. 6.—This electrocardiogram was obtained from an 8-year-old boy with coarctation of the aorta. Note the presence of right-axis deviation in a patient with a lesion producing hypertrophy of the left ventricle.

probably represents the projection on to V_1 of the change in direction of the horizontal vector just preceding the anterior return (Fig. 3).

2. *Left Ventricular Hypertrophy.*—Our approach to evaluating the electrocardiographic criteria for left ventricular hypertrophy is similar to that for right, but the results of the two groups stand in sharp contrast to each other. When applying Sokolow and Lyon's criteria for left ventricular hypertrophy[25] only 54 per cent of the patients of this series were found to have evidence of left ventricular hypertrophy. This per cent was further reduced when the strictest limits of normal voltage and ventricular activation time were applied. Then, only nine out of twenty-eight patients (32 per cent) had one or more abnormal findings (i.e., an S_{V1}, R_{V6}, S_{aVR}, or R_{aVL} greater than any normal, an R_{V1} less than any normal, or preintrinsicoid deflection in $V_6 \geqq 0.06$ sec., Fig. 4). The reason for the marked discrepancy between the frequency with which patients with right ventricular hypertrophy and those with left ventricular hypertrophy satisfied electrocardiographic criteria for ventricular hypertrophy are not clear at this time, but it is quite apparent that a large number of patients with left ventricular hypertrophy due to congenital heart disease will present with normal electrocardiograms.

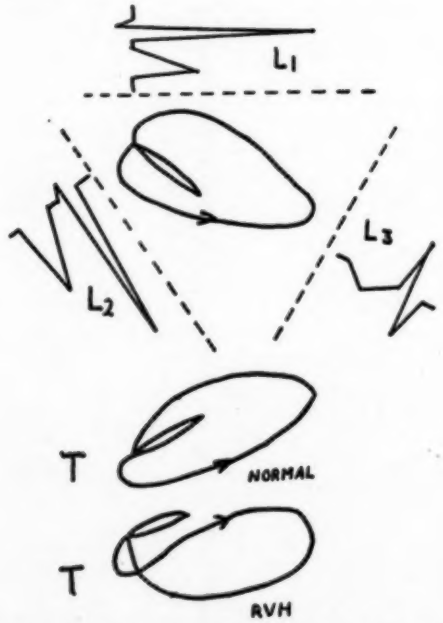

Fig. 7.—The lower portion illustrates the horizontal plane vector loops in the normal, and in right ventricular hypertrophy. Both vectors are associated with the same frontal loop and therefore the same standard leads, as pictured in the upper one-half of the figure. Thus, the mean electrical axes of the QRS may be identical in the normal and in right ventricular hypertrophy.

3. *Axis Deviation.*—Although earlier observers believed that abnormal deviation of the electrical axis, particularly when marked, is a reflection of ventricular hypertrophy,[37-39] more recent workers have indicated that mere positional changes of the heart can be responsible for alterations in axis deviation.[26,31,40-42] It is of interest that less than two-thirds of the patients with right ventricular hypertrophy presented with right-axis deviation, and less

than one-fourth of the patients with left ventricular hypertrophy had left-axis deviation. The presence of right-axis deviation in left ventricular hypertrophy and left-axis deviation in right ventricular hypertrophy was noted as well (Figs. 5 and 6).

The determination of electrical axis from standard leads as conceived by Einthoven and collaborators[43] is related to the projection of the vector loop on the frontal plane. Identical frontal plane projections, and hence identical electrical axis deviations, can be obtained with an anteriorly directed vector as in right ventricular hypertrophy, in a normal, or in a posteriorly directed vector as in left ventricular hypertrophy (Fig. 7). Thus, we feel, little diagnostic significance should be attached to the mean electrical axis of the QRS as presently obtained from the standard leads. The spatial orientation of the mean electrical axis of the ventricular excitation and recovery processes in all three planes may prove of considerably greater clinical significance.

SUMMARY AND CONCLUSIONS

1. Of 135 patients with congenital heart disease, in whom the diagnosis appears to be well established, sixty-six had malformations producing isolated right ventricular hypertrophy, while twenty-eight had lesions resulting in isolated left ventricular hypertrophy. Some of the existing criteria for ventricular hypertrophy were applied to the electrocardiograms of these patients.

2. The electrocardiographic criteria of Sokolow and Lyon for right ventricular hypertrophy are too broad to establish that diagnosis with reliability. While these criteria will pick out virtually every case of right ventricular hypertrophy (65 cases out of our series of 66) there will be normal subjects, particularly in the younger age groups, who will be incorrectly diagnosed as having right ventricular hypertrophy. These criteria are, however, useful for screening purposes.

3. The electrocardiographic diagnosis of ventricular hypertrophy may be made with reliability on the basis of abnormal voltages, or ventricular activation time only in the absence of an RSR′ pattern in V_1, conduction disturbances, or myocardial infarction. When the limits of voltage, or ventricular activation time obtained from the largest series of normal subjects broken down by age groups, are exceeded, the electrocardiographic diagnosis of ventricular hypertrophy may be made with reliability. We believe these to be the most satisfactory criteria now available.

4. By applying the above criteria to the fifty-one patients with lesions producing right ventricular hypertrophy, without an RSR′ pattern in V_1, the diagnosis was made in this manner in forty-one (80 per cent) but only in nine (32 per cent) of the twenty-eight patients with left ventricular hypertrophy.

5. The electrocardiogram cannot reliably distinguish incomplete right bundle branch block, right ventricular hypertrophy with RSR′ in V_1, and the RSR′ in V_1 seen occasionally in normal subjects. The spatial vectorcardiogram can clarify this problem.

6. Little diagnostic significance should be attached to the mean electrical axis obtained from the standard leads.

7. The electrocardiogram may be of considerable value in diagnosing the presence of right ventricular hypertrophy in congenital heart disease in a large percentage of cases, and in suggesting the possibility of the presence of right ventricular hypertrophy in almost all of the remainder. However, the electrocardiogram is of less value in left ventricular hypertrophy due to congenital heart disease, since it fails to pick out the majority of such cases.

SUMMARIO IN INTERLINGUA

Esseva obtenite electrocardiogrammas in un gruppo de 135 patientes con congenite morbo cardiac in qui le diagnose esseva clarmente establite. Varie existente criterios pro le diagnose de hypertrophia ventricular esseva applicate a iste electrocardiogrammas. Nulle de illos se monstrava integremente digne de confidentia.

Nos ha derivate criterios electrocardiographic—de un genere dignissime de confidentia in nostre opinion—ab le limites del voltage normal e del tempore de activation ventricular in derivationes precordial compilate per Kossmann in studios de un grande numero de individuos normal. Quando le limites que es valide pro un certe group de etate del patientes es excedite, il es permittite considerar le diagnose de hypertrophia ventricular como establite providite que le caso in question non involve ulle infarcimento myocardiac o ulle disturbation de conducto.

Le application de iste criterios a 51 patientes con hypertrophia dexteroventricular sin le configuration RSR′ in le derivation V_1 resultava in 41 diagnoses positive. In le caso de 28 patientes con hypertrophia sinistroventricular solmente 9 diagnoses positive esseva obtenite.

The cardiac catheterizations were performed by members of a team under the supervision of Dr. Alvin J. Gordon. The angiocardicgrams were performed by Dr. Sigmund A. Brahms.

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THE AXOSTAT

III. An Improved Form of the Instrument, and Its Application to the Establishment of Spatial Electrocardiographic Indices in 102 Normal Subjects

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IN PREVIOUS reports[1,2] we described a relatively simple instrument, referred to as the axostat, which when used in conjunction with a conventional electrocardiograph permitted multiaxial registration of the extremity leads of the electrocardiogram. Critical tests of the physical characteristics of the instrument demonstrated that it produced scalar electrocardiograms which represented the projection of the spatial vectorcardiogram on any axis of the various face planes of the Wilson tetrahedron.[3] It was further demonstrated in accordance with the principle set forth by Graettinger and associates[4] that the projection of a mean spatial vector in a given plane is directed at right angles to the angular position of the transition point (point at which the algebraic area under a given wave or complex is zero). On this basis we found[2] that the axostat could be employed to determine vector directions rapidly and with considerable precision because it divided the angular interval between the conventional extremity leads into any desired number of subdivisions, thus reducing the error involved in estimating the position of the transition point.

It is the purpose of this report to describe an improved form of the axostat which was employed to determine the orientation of the mean spatial QRS and T vectors of 102 normal, youthful subjects. The improved form of the instrument is somewhat more complicated in constructional details than the original model, but it has proved to be decidedly simpler and more reliable in its operation.

INSTRUMENTATION

The schematic diagram of the improved axostat is shown in Fig. 1. The heart of the instrument is a precision ring potentiometer (shown at the upper right of the figure) provided with three equally spaced taps, and two wiper arms which are 180° apart. Three electrocardiographic potentials derived from

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This work was supported by grants from the U. S. Public Health Service (National Heart Institute, H 1362 - C) and the Memphis Heart Association.

Received for publication Jan. 26, 1955.

the subject undergo one stage of identical vacuum tube amplification each as shown. The outputs of the amplifiers are reduced by means of identical voltage dividers and fed into the appropriate taps of the ring potentiometer. The potentials picked up by the two wiper arms of the potentiometer are fed into the input of a conventional electronic electrocardiograph.*

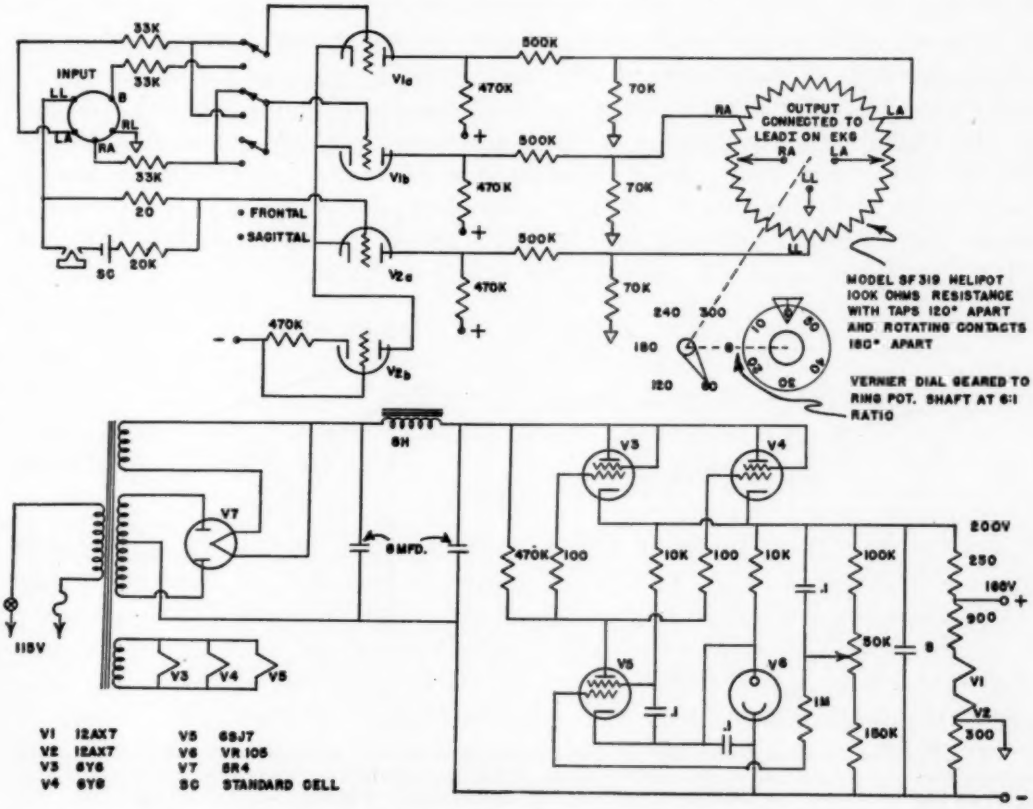

Fig. 1.—Schematic diagram of the improved axostat. The "heart" of the instrument is the precision potentiometer shown in the upper right-hand corner of the figure. The three taps are equally spaced on the potentiometer winding. The two wiper arms are oriented diametrically opposite from each other. The three triode amplifier sections, $V1_a$, $V1_b$, and $V2_a$, function as impedance transformers which eliminate errors due to unbalanced skin-electrode resistances. A close match of these three amplifier sections is essential. Further description in text.

The instrument is designed to record from either the frontal or sagittal plane of the subject. In recording from the frontal plane the electrocardiographic potentials are derived from both arms and the left leg of the subject. In recording from the sagittal plane the potentials are derived from an image point half-way between the two arms, from the left leg, and from the angle of the left scapula. The image point is produced by tieing the right and left arms together electrically with matched 33,000 ohm resistors.

The vacuum tube amplifiers play no primary role in the function of the instrument except that they eliminate the inaccuracies arising from skin resistance effects which proved rather troublesome in the original model. The

*Model EK-2, The Burdick Corporation, Milton, Wisconsin.

potentials introduced into the taps of the ring potentiometer are accurate replicas of the potentials derived from the subject, and the amplification achieved in each of the three triode sections is not critical as long as they are all identical.

The physical significance of the axostat leads can be readily explained on the basis of the simple geometric interpretation depicted in Fig. 2. In the case of frontal plane registration the ring potentiometer is shown as assuming the form of an equilateral triangle with the potentiometer taps forming the apices of the triangle. The position of the wiper arms is indicated by the points P_1 and P_2. The center of the triangle (point where the medians intersect) is formed by the 70,000 ohm components of the voltage dividers, and corresponds to the Wilson central terminal.[5] As demonstrated in the earlier report[1] the connection between the central terminal and each of the sliding contacts on the ring potentiometer has an associated lead vector indicated by the line segments P_1C and CP_2. These line segments add together, giving as the lead vector of a particular

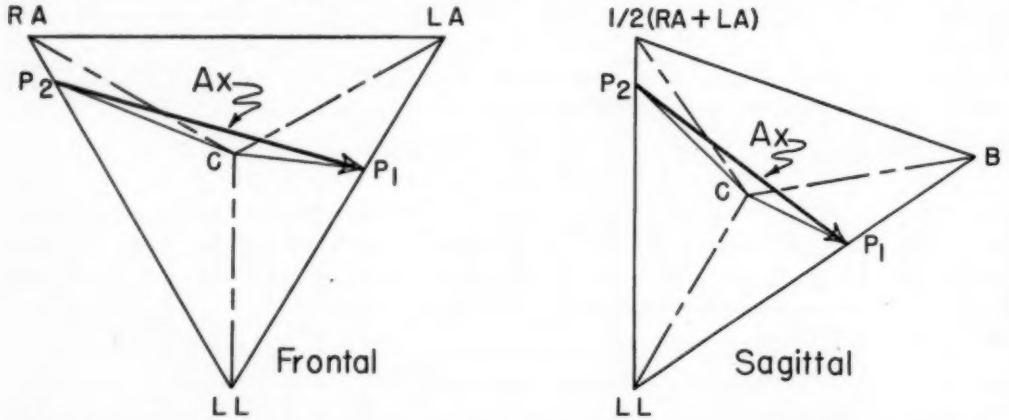

Fig. 2.—Geometric representation of the axostat network and its associated lead vectors in recording from the frontal and sagittal planes of the Wilson tetrahedron. The positions of the two wiper arms on the potentiometer winding are P_1 and P_2, respectively. The lead vector, Ax, associated with a given position of the wiper arms is a directed line segment joining the two points. In this illustration the position of the wiper arms is identical for both the frontal and sagittal plane connections. However, due to the geometry of the situation, the associated lead vectors are different. The angular position dials of the instrument are calibrated for the frontal plane connections, and a nomogram is employed to correct for the disparities between the dial reading and the direction of the lead vector in the sagittal plane.

axostat setting the line segment P_1P_2. The significance of the lead vector is that its direction defines the lead axis of a given axostat setting and that its length determines the "weight" of the lead.[6] It is evident therefore that rotation of the potentiometer shaft permits registration of scalar extremity electrocardiograms on any desired axis of the frontal plane of the Wilson tetrahedron. When the wiper arms are rotated so that the lead vector P_1P_2 is directed at 0°, 60°, or 120°, the corresponding axostat electrocardiograms are identical to Leads I, II, and III, respectively. When the lead vector is directed at −150°, −30° or 90°, the axostat tracings are identical in form to properly recorded unipolar extremity leads, but due to the physical characteristics of the potentiometer network the amplitude of the tracings is 15 per cent greater than the amplitude of Graettinger's vector unipolar leads.[4]

The angular position dial and its associated vernier control are calibrated on the basis of the Einthoven triangle[7] as a frame of reference. When the line joining the two contact points of the wiper arms is parallel to the sides of the triangle (for the purpose of recording the conventional Einthoven leads or their inverts) the physical position of the wiper arms corresponds exactly with the direction of the associated lead vectors. Therefore the coarse angular indicator (Fig. 1) is calibrated in 60° intervals. Within each of these intervals the correspondence between the physical position of the wiper arms and the orientation of the associated lead vectors is not exact except at the midposition of each interval. Therefore, the scale marks on the vernier dial are not equally spaced, the interval between the scale marks being determined by the principles outlined in Fig. 2.

In recording from the sagittal plane the same principles apply as in registration from the frontal plane. In the sagittal case, however, the ring potentiometer is represented as assuming the form of an isosceles triangle such as is shown in the right half of Fig. 2. Because of the differences in geometric representation between the two cases, the angular dial readings are incorrect when recording from the sagittal plane. However, a simple nomogram has been constructed which converts the nominal dial readings into the true position of the lead axes in the sagittal plane.

Tests with this instrument similar to those described with the original instrument[2] demonstrated the validity of the underlying physical principles within the limit of experimental error. In testing with an electrical dummy it was found that the transition point as determined with the instrument corresponded to within ½° of the theoretically predicted value. When an identical potential was impressed on each of the amplifier grids it was ascertained that the error vector produced in the potentiometer network had a magnitude of less than 0.2 per cent of the impressed potential. The 500,000 and 70,000 ohm resistors comprising the voltage dividers shown in Fig. 1 are wire-wound elements chosen with a great deal of care not only for close match of values (± 0.25 per cent) but also for low noise level. The amplifier tubes also were carefully selected on the basis of good match of amplification factors and low noise level. Checking the network balance at the beginning and end of each day's use showed that the instrument functioned reliably and accurately over a period of several months.

METHOD OF STUDY

The electrical fields generated by the heart were "explored" by means of the axostat in the frontal and sagittal planes of 102 normal youthful adult subjects chosen from the medical student, student nurse, and intern population of our teaching hospital. Fifty of the subjects were females and fifty-two were males. The age range of the female subjects was 17 to 33 years with a mean value of 20.5 years and a standard deviation of 3.1 years. The age range of the male subjects was 21 to 35 years with a mean value of 26.8 years and a standard deviation of 3.5 years. The classification of normality was based on repeatedly

negative student health examinations including a normal cardiac silhouette on the roentgenogram of the chest. Very little special preparation of the subjects was observed except that all tests were made at least two hours postprandially, the subjects did not undergo any vigorous physical exertion prior to the test, and they rested in the recumbent position for 20 minutes immediately before the tracings were made.

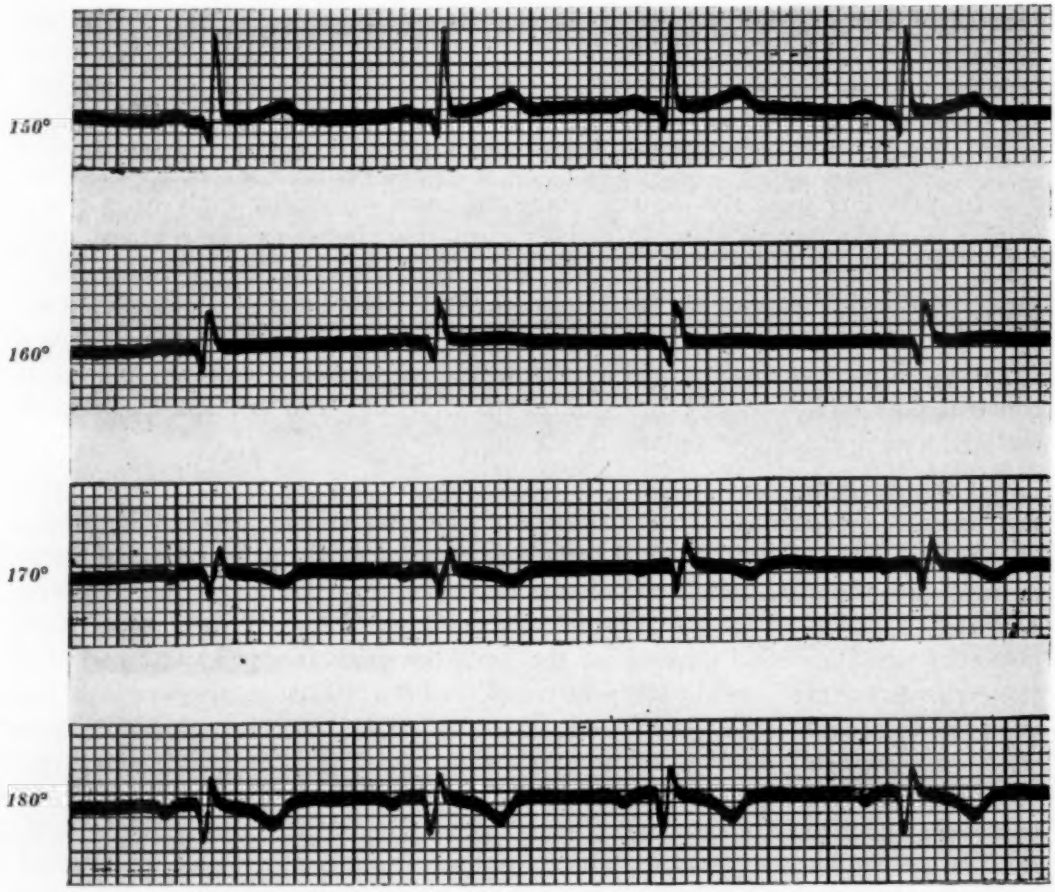

Fig. 3.—Axostat tracings recorded from the frontal plane of a normal subject. Inspection of the tracings reveals that the QRS complex is very close to transition at 170°, and that the T wave is very close to transition at 160°. In this case the direction of the mean QRS and T vectors is determined by subtracting 90° from the observed positions of transition. This method of surveying the electromotive forces of the heart in the frontal and sagittal planes permits rapid estimation of the direction of mean electrical vectors to the nearest 5° position. Further discussion in text.

The method of exploration consisted of recording a scalar electrocardiogram for each 10° position of lead axis in both the frontal and sagittal planes. A typical set of tracings covering the region of 150° through 180° in the frontal plane is shown in Fig. 3. As can be seen from an examination of this figure, it is rather easy to estimate transition points to the nearest 5° of axial position (± 2½° accuracy) by simple visual inspection of the tracings. A few of these estimations which proved more difficult to make will be discussed later. In most instances, of which Fig. 3 is representative, the direction of the projections

of the mean spatial vectors was determined by subtracting 90° from the angular position of their transition points. In a few cases it was necessary to add 90° to the transition point position in order to determine the direction of the mean vector projection.

The directions thus determined were referred to an orthogonal Cartesian frame of reference in which the OY axis is the line of intersection of the frontal and sagittal planes. The OX and OZ axes are horizontally oriented, lying in the frontal and sagittal planes, respectively. The OX axis is positive toward the subject's left, the OY axis toward the feet, and the OZ axis toward the back. Angular positions in the frontal plane, labeled a, are measured downward from the positive half of the OX axis; angular positions in the sagittal plane, labeled b, are measured downward from the positive half of the OZ axis. The direction cosines L, M, and N which orient the spatial vectors with respect to the OX, OY, and OZ axes, respectively, are calculated from the formulas $L = (\cot a)/D$, $M = 1/D$, and $N = (\cot b)/D$, where $D^2 = \cot^2 a + \cot^2 b + 1$.* The angle, θ, between the mean spatial QRS and T vectors is determined from the well-known formula

$$\cos \theta = L_{QRS}L_T + M_{QRS}M_T + N_{QRS}N_T.$$

RESULTS

The axostat tracings derived from the frontal plane were carefully compared with the conventional extremity leads. In all instances leads recorded on the 0°, 60°, and 120° axes were virtually identical to the corresponding Einthoven leads. This identity was particularly striking when the leads were at or near the transition point. On the other hand the form of the tracings recorded at −150°, −30°, and 90° did not always agree well with the corresponding augmented unipolar extremity leads, aV_R, aV_L and aV_F.[9] In many cases the axis of the aV lead appeared to have been rotated 10° or more from its anticipated position. These disparities were undoubtedly due to imbalances in skin resistances in the registration of the aV leads, and are in accord with the recently published observations of Schwarzschild and associates.[10] As anticipated, there was excellent agreement in each case between the 90° axostat tracing recorded in the frontal plane as compared to the 90° tracing recorded in the sagittal plane.

Employing the methods and formulas described in the preceding section, the following planar electrocardiographic indices were determined in all of the subjects: direction of the mean QRS vectors in their frontal and sagittal projections, direction of the mean T vectors in their frontal and sagittal projections, angular differences between the mean QRS and T vectors in the frontal and

*These formulas, although somewhat different from those of Helm,[8] are very similar in form and principle of derivation. Therefore, their derivation is omitted in this paper. We employ them in preference to Helm's because they are better adapted for use with calculators having the feature of accumulative and repetitive multiplication. In the unusual circumstance of the spatial vector lying in the horizontal plane these formulas yield indeterminate results. In this event alternative formulas, previously published, may be employed.[2]

sagittal projections. In addition, the angle between the mean spatial QRS and T vectors was calculated. The results of these determinations are summarized in Table I.

TABLE I. SUMMARIZATION OF PLANAR ELECTROCARDIOGRAPHIC INDICES AND ANGLES BETWEEN MEAN SPATIAL VECTORS AS DETERMINED ON 102 NORMAL SUBJECTS

ELECTROCARDIOGRAPHIC INDEX	PROJECTION	AVERAGE VALUE (DEGREES)	STANDARD DEVIATION (DEGREES)
Direction of mean QRS	Frontal	62.9	±22.4
	Sagittal	52.1	±19.7
Direction of mean T	Frontal	52.0	±17.1
	Sagittal	58.6	±19.9
Direction of mean QRS minus direction of mean T	Frontal	10.9	±21.0
	Sagittal	− 6.3	±21.0
Angle between mean spatial vectors	——	22.0	±12.1

In conformity with clinical experience the direction of the mean QRS and T vectors in the frontal plane exhibited a considerable degree of scatter. The degree of scatter was approximately the same for the direction of these vectors in their sagittal projections, and for the angular difference between the QRS and T vectors in both their frontal and sagittal projections. In the case of the spatial angle between vectors the degree of scatter proved to be significantly less than in the case of the planar indices.

The statistical significance of the planar indices may be greatly enhanced by treating the projections of a vector on the frontal and sagittal planes as interrelated rather than disparate pieces of information. The results of this type of analysis are exemplified in Figs. 4 and 5. Fig. 4 is a scattergram for the mean spatial QRS vectors in which the angle of the sagittal projections is plotted as the dependent variable, and the angle of the frontal projections as the independent variable (b_{QRS} vs. a_{QRS}). Fig. 5 is the same type of scattergram for the mean spatial T vectors (b_T vs. a_T). The linear trend lines (regression lines) in the two figures were fitted by the method of least squares. The broken lines in the figures are plotted one standard deviation to either side of the regression lines.

The results of these analyses may be summarized by the equations of the regression lines, the standard deviations (S.D.), and the coefficients of correlation (r).

1. Direction of mean QRS in sagittal plane vs. direction of mean QRS in frontal plane; $b_{QRS} = 7.1 + 0.72a_{QRS}$; S.D. = 10.2°; r = 0.85
2. Direction of mean T in sagittal plane vs. direction of mean T in frontal plane; $b_T = 4.8 + 1.03a_T$; S.D. = 11.3°; r = 0.82

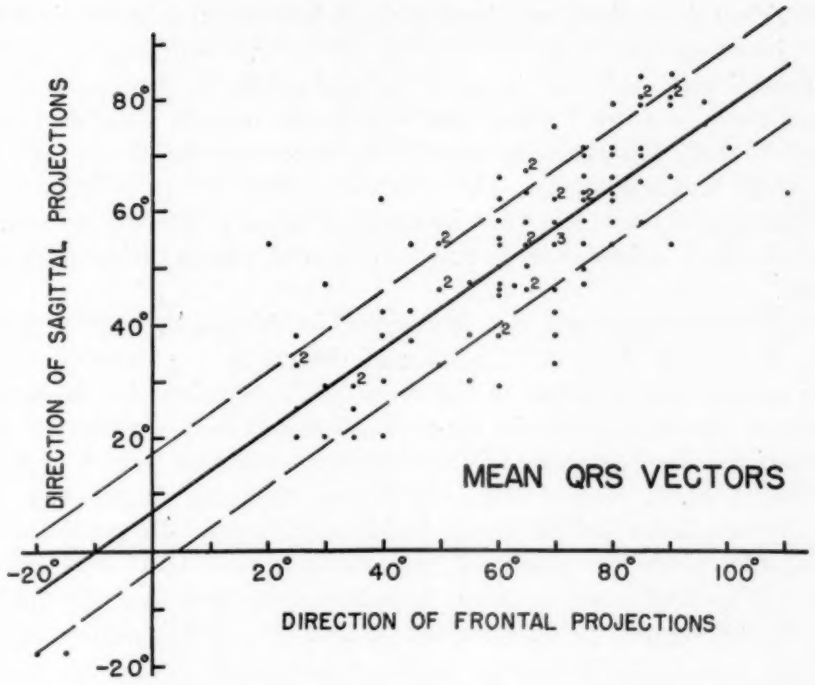

Fig. 4.—Scattergram illustrating the relationship of the mean QRS vector directions in the sagittal plane to the direction of the same vectors in the frontal plane. The linear trend line is plotted according to the method of least squares. The broken lines are plotted one standard deviation to either side of the mean trend line.

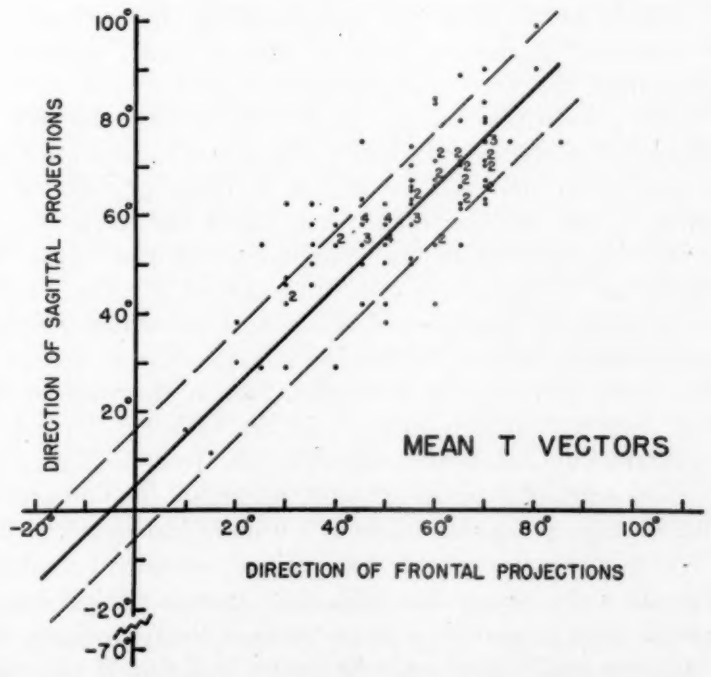

Fig. 5.—Scattergram illustrating the relationship of the mean T vector directions in the sagittal plane to the direction of the same vectors in the frontal plane. The method of curve fitting is the same as that employed in Fig. 4.

It is evident from these relationships and from Figs. 4 and 5 that a highly significant interdependence exists between the frontal and sagittal projections of mean spatial vectors in our group of normal subjects. Comparison of these figures with those in Table I shows that the scatter of data about the regression lines is significantly less than the scatter of the same data about their average values. These findings suggest the conclusion that the criteria of normality of mean QRS and T orientation can be rendered more precise by a consideration of their projections in both the frontal and sagittal planes rather than in either plane alone.

Three other scattergrams, not reproduced in this paper, were prepared and analyzed. In one of them the direction of the mean T vectors in the frontal plane was plotted as a function of the mean QRS directions in the same plane. The scatter of the data about the regression line was only slightly less than the scatter about the average value of the dependent variable (standard deviations $\pm$ 18.4° and $\pm$ 21.0°, respectively), indicating that the relationship between these particular planar indices is not highly significant. In a similar analysis for the sagittal plane the standard deviations were $\pm$ 18.1° and $\pm$ 21.0°, respectively. This slight improvement in scatter indicated that the QRS and T directions in the sagittal plane were not related in a highly significant manner either.

In the final plot the angle between the mean spatial QRS and T vectors was represented as a function of the direction of QRS in the frontal plane. The slope of the regression line (regression coefficient of correlation) was found to have the rather small value of -0.106. The scatter of data about the regression line was only slightly better than the scatter about the average value of the spatial angle (standard deviations $\pm$ 11.6° and $\pm$ 12.1°, respectively). The conclusion drawn from this analysis is that the angle between the mean spatial QRS and T vectors constitutes a spatial electrocardiographic index which is virtually independent of the orientation of the mean spatial QRS vector.

The data were also analyzed by means of frequency distribution tables charted according to the sex and bodily habitus of the subjects. Table II is such a table showing the frequency distribution of the angle between the mean spatial QRS and T vectors in class intervals of 5°. On the basis of this type of analysis it appeared that mean QRS vectors are oriented somewhat more vertically (approximately 10°) in slender individuals than in persons of average bodily habitus. This difference is somewhat less in the case of the mean T vectors. There were not enough subjects in the asthenic, athletic, and obese categories to warrant any conclusions regarding the relationship of mean vector orientation to these particular types of bodily habitus. The differences between the slender and average groups of subjects are more indicative of a trend than a conclusion which will withstand a fine-grained statistical analysis. Nevertheless, these findings are compatible with the common clinical impression that slender individuals tend to exhibit a more vertical electroposition than persons of average or athletic bodily habitus. As shown in Table II the angle between the mean spatial QRS and T vectors is virtually independent of the sex and bodily habitus of the subjects.

TABLE II. FREQUENCY DISTRIBUTION OF ANGLE BETWEEN MEAN SPATIAL QRS AND T VECTORS ACCORDING TO SEX AND BODILY HABITUS

ANGLE (DEGREES)	BODILY HABITUS										TOTAL
	ASTHENIC		SLENDER		AVERAGE		ATHLETIC		OBESE		
	M	F	M	F	M	F	M	F	M	F	
5	—	—	1	1	2	2	—	1	—	1	8
10	—	—	2	2	2	4	1	—	1	1	13
15	—	—	6	2	5	7	1	—	1	1	23
20	1	—	2	2	3	6	1	—	—	—	15
25	1	—	2	1	5	3	1	—	1	1	15
30	—	—	—	6	4	2	—	—	2	1	15
35	—	—	—	—	1	1	1	—	—	—	3
40	—	—	—	3	—	—	—	—	—	—	3
45	—	—	1	1	—	—	—	—	1	—	3
50	—	—	—	1	—	—	—	—	—	—	1
55	—	—	—	—	—	—	—	—	1	—	1
60	—	—	—	—	—	—	—	—	—	—	—
65	—	—	—	—	2	—	—	—	—	—	2
											102

DISCUSSION

Instrumentation.—The axostat, in the improved form described in this paper, provides a rapid, simple, and relatively precise method for determining the directions of mean QRS and T vectors in the frontal and sagittal electrocardiographic planes of the body. The technical demands involved in operating the device are not much greater than those required in conventional electrocardiography. Employing the instrument for this purpose almost completely eliminates the need for laborious and questionably accurate determination of the areas under electrocardiographic waves and complexes. Our routine method of determining the angular positions of transition points is somewhat more precise than the original method described by Graettinger and associates[4] inasmuch as it divides the 30° intervals of the hexaxial reference system into three equal subdivisions. This procedure reduces the magnitude of error in estimating the position of transition points and facilitates such estimation to the nearest 5° position in the reference system. In many cases this precision can be further increased by recording at even smaller angular subintervals. However, increasing the precision of estimation in this manner involves a considerable amount of additional labor which, in view of the scatter of our data, hardly seems justified.

The ability of the axostat to resolve the position of transition depends to some extent upon the magnitude of the recorded potentials and upon the shape of the associated vector loops. Large potentials tend to produce a more sharply defined transition point than smaller potentials. Similarly, the position of the transition point is more critical with long narrow vector loops than with vector

loops which are approximately circular or cardioid in shape. In this paper a total of 408 transition points was estimated. Of this number, 392 determinations were made with the desired precision by simple visual inspection of the tracings. In twelve estimations rather close and painstaking visual inspection was required. Only in the remaining four instances was it necessary to "count squares" in the vicinity of the transition point in order to estimate its position. In all of these instances the area-estimating procedure was a fairly quick and simple one because the complexes were of relatively small magnitude.

Another reason that the axostat method of determining transition points is more accurate than Graettinger's original method lies in the fact that the instrument eliminates rotation of lead axes which may result from unbalanced skin resistances. Our experience in this respect parallels that of Schwarzschild and associates,[10] who demonstrated that significant rotation of the unipolar extremity lead axes may result from such unbalances. On this basis a number of our transition points determined from the conventional electrocardiograms were as much as 10° in error when compared to the axostat determination.

Frame of Reference.—In analyzing the instantaneous and average electrical vectors generated by the activity of heart muscle, it is desirable to orient these vectors within a mutually orthogonal set of Cartesian axes such as was described earlier in this paper. In order to accomplish this purpose numerous frames of reference have been proposed. In a number of these the conventional Einthoven connections have been employed to establish the frontal plane of the reference system. In order to establish a plane which is normal to the frontal plane, one or more additional electrodes have been employed. Representative of such schemes are the use of a back electrode in the formation of the Wilson tetrahedron,[3] the sagittal plane connections of Arrighi,[11] and the horizontal plane connections of Cossio and Bibiloni.[12] In still other arrangements the conventional frontal plane connections may be abandoned altogether and an entirely new frame of reference such as the single cube[13] or the trirectangular trihedron[14] substituted. Finally, the conventional frontal plane connections may be retained, and a multiplicity of electrode positions on the thorax employed to determine the components of the heart vector normal to the frontal plane.[15,16]

Although it is doubtful that any of these systems provides anything more than a rough approximation of the desired set of axes,* it is certain that some of them are useful as a spatial frame of reference in much the same manner that the Einthoven triangle has proved valuable as a planar frame of reference. Some of the other schemes, however, introduce certain incompatibilities and had probably best be abandoned. An example of such an incompatible system is the combination of the Einthoven and Arrighi triangles. In this arrangement there is no guarantee that the scale factors and orientation of the nominal vertical axes are identical for both the frontal and sagittal plane connections. Thus the two types of connections may be expected to record different "vertical" components.

*For a critical evaluation of some o these systems see Frank,[17,18] and Brody and Romans.[19,20]

In this paper we have employed the Wilson tetrahedron as a frame of reference because (a) it introduces no incompatibilities between the frontal and sagittal plane connections, (b) it obviates the need for electrocardiographic registration from multiple thoracic positions, and (c) it renders the frontal plane analysis of our data strictly applicable to conventional extremity lead electrocardiography. It is virtually certain that the Wilson tetrahedron is decidedly nonequilateral.[21,22] If the configuration of the Wilson tetrahedron is ever determined with a reasonable degree of accuracy, it should be possible to apply correction factors to our present and future data and thus produce normalization of our axes. From the clinical point of view the primary purpose of such normalization would be the possibility that the scatter of spatial vector data would be reduced. If such reduction of scatter did not result the equilateral tetrahedron would be as suitable for clinical purposes as the corrected frame of reference.

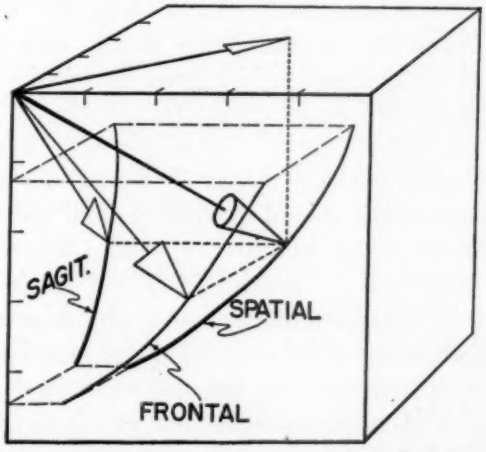

Fig. 6.—Three-dimensional representation of the locus of mean spatial QRS vectors. The spatial curve is derived from the linear trend line shown in Fig. 4. This illustration demonstrates that the mean QRS vectors of normal subjects are not randomly oriented in space but tend to follow a well-defined curve of orientation. A similar curve, not shown here, also may be obtained in the case of the mean spatial T vectors. To avoid confusion in the illustration, the entire spatial locus is not reproduced in this figure.

Spatial Electrocardiographic Indices.—As shown in Table I the electrocardiographic indices for the sagittal plane (direction of mean QRS and T vectors, angular difference between QRS and T vectors) exhibit essentially the same amount of scatter as they do in the frontal plane. In this respect at least, very little seems to be gained by recording electrocardiograms from a plane which is normal to the frontal plane. However, our method of analysis demonstrates that highly significant relationships exist between the two sets of planar electrocardiographic indices. On the basis of these relationships it is possible to establish a set of spatial electrocardiographic indices which may prove superior to the planar indices because of reduced scatter.

Two of these relationships are demonstrated in Figs. 4 and 5 where it is seen that the projections of mean spatial vectors on the frontal and sagittal planes are mutually dependent rather than independent entities. The geometric significance of these relationships in the case of mean spatial QRS vectors

is illustrated in Fig. 6. It is seen in this figure that the mean spatial QRS vectors tend to pass through a well-defined spatial curve or locus. Similarly, the mean spatial T vectors tend to pass through another, equally well-defined locus. It is apparent from Equation 2 that this locus will very nearly be the arc of a great circle whose plane is approximately perpendicular and bisects the angle XOZ of the coordinate frame.

Another spatial relationship which exhibits significantly less scatter than the planar indices is the angle between the mean spatial QRS and T vectors. It is seen in Table II that 89 (87.3 per cent) of the subjects had a spatial angle of 30° or less. By comparison, the angular positions of 89 mean QRS vectors in the frontal plane occupied a range of 30° to 95°; the range for the frontal projections of the mean T vectors was 30° to 75°; and the range for the angular differences between the frontal projections of the mean QRS and T vectors was −10° to 50°. The relative constancy of the spatial QRS − T angle and its virtual independence of electrocardiographic electroposition, sex, and bodily habitus was not altogether unanticipated since the spatial angle should reflect the order of myocardial repolarization in comparison to the order of depolarization.

Thus in recording electrocardiograms from both the frontal plane and a plane approximately normal to the frontal plane, we have established a set of spatial electrocardiographic entities in our group of normal individuals which cannot be obtained from conventional extremity lead electrocardiograms alone. These entities are (a) the locus of mean spatial QRS vectors; (b) the locus of mean spatial T vectors; (c) the spatial QRS − T angle. We anticipate that further determinations of this sort both in normal subjects and in persons with heart disease will provide us with a set of three spatial electrocardiographic indices which will prove superior to the corresponding planar indices. For one thing, analysis of this type accounts for the fact that the electromotive forces generated by the heart are actually of a 3-dimensional rather than a 2-dimensional nature. What is probably even more important, there is significantly less scatter of the spatial indices than of the corresponding planar indices. On the basis of a priori reasoning it seems almost certain that this reduction of scatter should render the criteria of normality and abnormality more exact than is the case with the more conventionally employed frontal plane indices. At the present time this thesis is being tested in a group of patients with hypertrophy and/or strain of one or both ventricles.

SUMMARY

An electrocardiographic instrument, known as the axostat, is described which provides a simple method for rapid and accurate determination of the directions of mean QRS and T vectors in their frontal and sagittal projections without the need for planimetric evaluation of areas under electrocardiographic deflections. Such determinations were made in a group of 102 normal, youthful adults, and the orientation of the mean spatial QRS and T vectors was calculated from these data.

The validity of several types of spatial electrocardiographic connections is discussed. Probably none of the associated frames of reference are accurate

from the standpoint of strict geometric interpretation, but undoubtedly some of them will prove useful for the interpretation of electrocardiographic data. Other frames of reference should be discarded because they introduce certain incompatibilities. The Wilson tetrahedron is employed in this study because it introduces no such incompatibilities, the associated lead connections are simple and easily reproduced, and the frontal plane components of our spatial data are directly applicable to conventional extremity lead electrocardiography.

The directions of mean QRS and T vectors in our group of normals display as much variability in the sagittal plane as they do in the frontal plane. However, the two sets of data are interrelated in a highly significant manner. Analysis of these relationships strongly suggests that three spatial electrocardiographic indices be firmly established and further investigated: (a) the locus of the mean spatial QRS vector, (b) the locus of the mean spatial T vector, and (c) the angle between the mean spatial QRS and T vectors. The primary virtue of these spatial indices appears to be reduced variability in the range of normal values. According to the standard deviations in our group of normals the scatter of the spatial electrocardiographic indices about their average values is reduced to almost one-half the scatter in the case of the corresponding planar indices. It is anticipated that this reduction in scatter will result in more precise criteria of normality and abnormality.

SUMMARIO IN INTERLINGUA

Le axostato es un instrumento electrocardiographic que permitte le registration del fortias electromotive del corde como projectiones scalar super qualcunque axe del planos frontal o sagittal del tetrahedron de Wilson. Es describite un forma meliorate del instrumento. Illo esseva empleate pro le rapide determination del orientation spatial de vectores median QRS e T in 102 normal adultos de etate juvene. Le analyse del datos assi obtenite monstra que 3 entitates spatial—(1) le loco del vector spatial QRS median, (2) le loco del vector spatial T median, e (3) le angulo inter le vectores spatial QRS e T median—exhibi un variabilitate significativemente inferior al variabilitate del correspondente frontal o sagittal projectiones planar. Es proponite que iste entitates sia utilisate como indices spatio-electrocardiographic in le expectation que illos providera plus precise criterios de normalitate e anormalitate que le methodos conventional nunc in uso.

The author is indebted to Mr. William E. Romans, Mr. B. P. McKay, and Mr. Gardner Ruffin for assistance in the design of the axostat, and for constructing the instrument. Mrs. Joyce Sarg served as technical assistant in performing the axostat surveys on our subjects. Miss Marzette Smith assisted with the calculations and the statistical analyses. Mr. Edward O. White assisted with the preparation of the illustrations.

ADDENDUM

Since this paper was prepared for publication, our attention has been called to a report by Selvini and associates[23] in which the authors describe a method for recording the electrocardiogram at axis intervals of 10° in the frontal plane.

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LEVARTERENOL BITARTRATE (LEVOPHED) IN THE TREATMENT OF CARDIAC ARRHYTHMIAS

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INTRODUCTION

PAROXYSMAL tachycardias of various kinds are common medical emergencies. In most cases, simple methods of treatment, such as carotid sinus pressure, eyeball pressure, or sedation are sufficient to restore normal rhythm. A certain number of cases, however, do not respond or become refractory to these measures. The tachycardia may persist so long that myocardial damage or congestive failure ensues. A small percentage rapidly develops hypotension and peripheral vascular collapse. These patients require more drastic therapy with digitalis, quinidine, or procaine amide. These drugs, even when administered by the intravenous route, at times require a long period to effect a conversion to sinus rhythm.

The chance clinical observation that a paroxysmal tachycardia was arrested by an intravenous infusion containing levarterenol* (Case 1) prompted the authors to investigate its usefulness in various paroxysmal arrhythmias.

Brief reports of eight cases are presented in which levarterenol seemed instrumental in slowing the abnormal rhythm or in restoring normal sinus rhythm.

METHOD

Patients with paroxysmal tachycardia, which did not respond to carotid sinus pressure and other simple methods of treatment, and whose blood pressures were not markedly elevated, were selected.

In all cases an electrocardiographic diagnosis was made prior to the administration of the levarterenol infusion. Continuous electrocardiographic control was maintained and blood pressures were recorded at 1 to 3 minute intervals while the drug was being administered. Parenteral procaine amide and digitalis preparations were kept close at hand during the procedure. The levarterenol was administered intravenously at a rate of 20 to 40 drops per minute in a concentration of 8 to 16 mg. per 1,000 c.c. of 5 per cent glucose in water. The rate of flow was adjusted to raise the systolic pressure to 120 to

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Received for publication Feb. 28, 1955.

*Levophed bitartrate, brand of levarterenol bitartrate (*l*-arterenol, *l*-norepinephrine), Winthrop-Stearns, Inc., New York, N. Y.

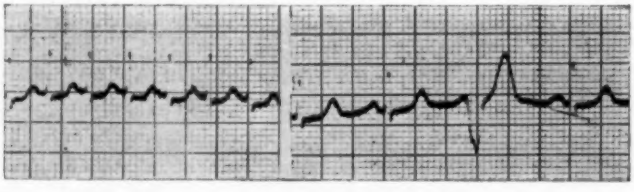
160 mm. Hg as quickly as possible. In all cases which demonstrated a response, this was achieved within a few minutes. After sinus rhythm was restored, the infusion was slowed to 10 to 20 drops per minute, and in most cases was terminated shortly thereafter.

CASE REPORTS

CASE 1.—A.L., a 43-year-old, white, American female, was admitted to the Long Island College Hospital on Aug. 2, 1953, because of severe precordial pain and dyspnea of five hours' duration. The patient had had hypertension for several years, with a systolic pressure averaging 180 to 200 mm. Hg. On the day of admission, following a heavy meal, there was the sudden onset of substernal pain radiating to the left shoulder and arm. Meperidine and oxygen were administered at home but they brought no relief. The patient was consequently brought by ambulance to the Long Island College Hospital.

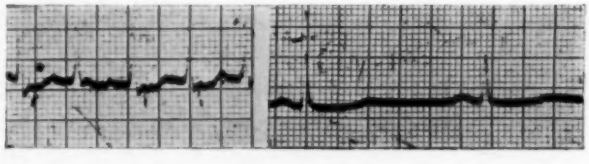
On admission the patient was noted to be an obese female, orthopneic, sweating profusely, and apparently in great pain. Fine, moist râles were heard at both lung bases; the pulse was imperceptible and the blood pressure unobtainable. An electrocardiogram taken at this time revealed a supraventricular tachycardia at a rate of 240 per minute (Fig. 1,*A*). Because of peripheral vascular collapse, an infusion containing 8 mg. of levarterenol in 1,000 c.c. of 5 per cent glucose in water was begun. Unfortunately, a continuous electrocardiogram was not recorded. However, an electrocardiogram taken minutes after the levarterenol was commenced showed reversion to normal sinus rhythm at a rate of 100 beats per minute with occasional premature ventricular contractions (Fig. 1,*B*). The blood pressure recorded at this time was 170 mm. Hg systolic. The patient also noted at this time complete disappearance of the pain and dyspnea. The levarterenol was continued for several hours at a slower rate and the blood pressure was maintained at 120 to 150 mm. Hg systolic.

The patient was subsequently digitalized and discharged on the fifth hospital day after repeated electrocardiograms failed to show any evidence of myocardial damage.



A. *B.*

Fig. 1.—Case 1. A.L. *A*, Supraventricular tachycardia, rate 240 beats per minute. *B*, Regular sinus rhythm after *l*-norepinephrine therapy. Rate 100 beats per minute with premature ventricular beat.



A. *B.*

Fig. 2.—Case 2. C.T. *A*, Supraventricular tachycardia, rate 160 beats per minute. *B*, Regular sinus rhythm after infusion of *l*-norepinephrine. Rate 52 beats per minute.

CASE 2.—Mrs. C.T., a 66-year-old, white female, was admitted to the Medical Service of the Long Island College Hospital for the third time on March 15, 1954, at 2:30 A.M. complaining of palpitation and chest pain of 8 hours' duration. The patient had a 10-year history of recurrent

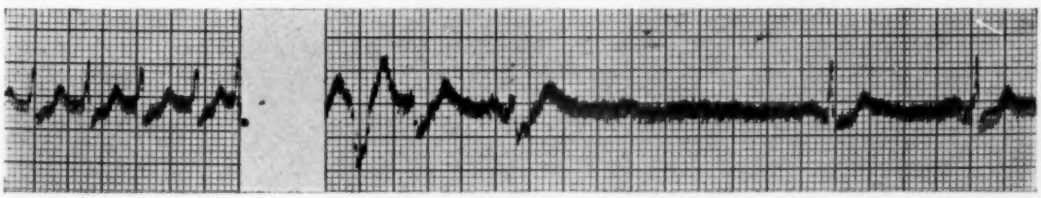
bouts of rapid heart action. She had been admitted five years previously with tachycardia and in shock; she was readmitted two years previously in similar circumstances. The patient continued to have recurrences lasting one-half to four hours. She had had three episodes at home in the preceding month. The patient had been taking quinidine and then procaine amide without much benefit.

On the present admission the apical rate was 160 beats per minute, blood pressure 70/60 mm. Hg, respirations 30 per minute, and temperature 98° F. Superficial physical examination at this time revealed peripheral coolness and clamminess; there were no signs of cyanosis or congestive heart failure. An electrocardiogram taken at this time revealed supraventricular tachycardia, probably of nodal origin, at a rate of 160 per minute (Fig. 2,*A*). Cedilanid, 0.4 mg., was given intravenously and an intravenous infusion of 8 mg. of levarterenol in 1,000 c.c. 5 per cent glucose in water was begun. The blood pressure rose to normal levels within a few moments, and at this point the rhythm was restored to regular sinus rhythm at a rate of about 52 beats per minute (Fig. 2,*B*). Within an hour the blood pressure was stabilized at 120/80 mm. Hg, and it was possible to discontinue the infusion.

She was placed on oral quinidine and discharged soon after a thorough study disclosed only mild hypertensive cardiovascular disease.

CASE 3.—T.L., a 62-year-old, white male, was admitted to the Medical Service of the Long Island College Hospital on May 18, 1954 complaining of palpitation. This had started suddenly while the patient was at work, and, after it had persisted for several hours, caused him to seek medical attention.

On admission the patient appeared to be in no acute distress. The general physical examination was negative except for a tachycardia of 185 per minute and a blood pressure of 74/60 mm. Hg. An electrocardiogram taken at this time showed the tachycardia to be of supraventricular origin (Fig. 3,*A*). The patient was given 1.2 mg. of lanatoside "C" intravenously and 100 mg. of Meperidine intramuscularly. After fifteen minutes there was no noticeable change in the cardiac rate or blood pressure. Accordingly, an infusion of 1,000 c.c. of 5 per cent glucose in water containing 16 mg. of levarterenol was started. The systolic blood pressure quickly rose to normotensive levels, and at that point there was a transient episode of ventricular fibrillation followed by a momentary period of asystole and then immediate reversion to sinus rhythm at a rate of 68 per minute (Fig. 3,*B*). The patient experienced no subjective complaint during the transitional period, and the sensation of palpitation and weakness disappeared immediately on reversion to sinus rhythm.



A. *B.*

Fig. 3.—Case 3. T.L. Representative portions of a continuous electrocardiogram. *A*, Supraventricular tachycardia at a rate of 185 beats per minute. *B*, Ventricular arrhythmia with a short period of asystole and prompt reversion to sinus rhythm at a rate of 68 beats per minute.

The levarterenol infusion was discontinued within an hour, and the patient was placed on prophylactic quinidine medication. Subsequent electrocardiograms were completely normal, and the patient was discharged on the eighth hospital day.

CASE 4.—G.M., a 47-year-old, white, male bartender, was admitted to the Medical Service of the Long Island College Hospital for the seventh time because of chest pain and palpitation on Aug. 29, 1954. The patient had a familial history of hypercholesterolemia and arteriosclerotic heart disease. He had been having attacks of supraventricular tachycardia since the age of 13.

He was usually able to terminate these attacks by eyeball pressure, self-induced vomiting, or anal sphincter tension. The last episode which had required hospitalization was three years prior to the present admission. He was admitted via the Emergency Room in acute distress, pallid, sweating, and complaining of severe chest pain.

A superficial physical examination showed a very rapid pulse, a blood pressure of 60/0 mm. Hg and a respiratory rate of 32 per minute. An electrocardiogram revealed a supraventricular tachycardia at a rate of 185 per minute (Fig. 4). An intravenous infusion of 8 mg. of levarterenol bitartrate in 500 c.c. of 5 per cent glucose in water was begun immediately. As his pressure rose, he complained of severe headache and a sense of impending disaster. This coincided with the appearance of the transient ventricular fibrillation in the continuous electrocardiogram (Fig. 4). The ventricular fibrillation lasted for a 3-second period and was followed by sinus rhythm. The levarterenol infusion was continued throughout the episode of ventricular fibrillation. When sinus rhythm returned the patient felt completely relieved; after 5 to 10 minutes the levarterenol infusion was discontinued and the blood pressure remained stabilized at 110/70 mm. Hg. At no time was a pressure over 120/80 mm. Hg recorded following his reversion to regular sinus rhythm.

Subsequent studies on this patient, including serial electrocardiograms, blood lipid and cholesterol determinations, were negative and the patient was discharged asymptomatic.

CASE 5.—Mrs. S.C., a 60-year-old housewife, was admitted on Sept. 23, 1954, to the Gynecological Service of the Long Island College Hospital for elective repair of a cystocele and rectocele.

Physical examination on admission was within normal limits except for a marked rectocele and moderate cystocele. The blood pressure was 120/80 mm. Hg and the pulse rate 76 per minute. The patient gave a history of intermittent treatment with digitalis and quinidine over the last 3-year period on account of paroxysmal attacks of cardiac arrhythmia.

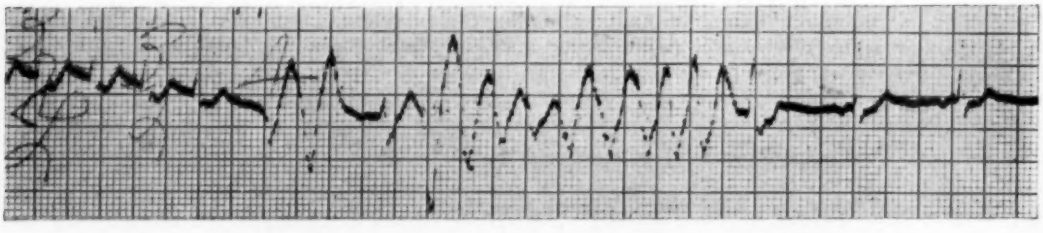
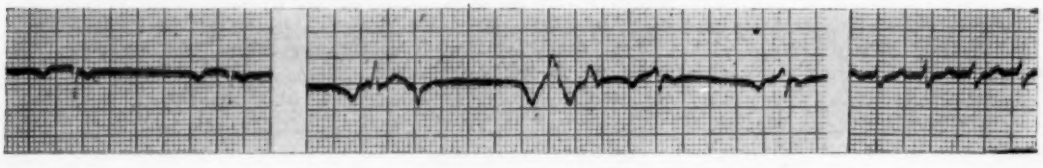


Fig. 4.—Case 4. G.M. Continuous electrocardiogram showing a supraventricular tachycardia at a rate of 185 beats per minute, transient ventricular fibrillation, and reversion to regular sinus rhythm at a rate of 100 beats per minute.



A. *B.* *C.*

Fig. 5.—Case 5. S.C. *A*, Supraventricular tachycardia at a rate of 166 beats per minute. *B*, Regular sinus rhythm with multiple premature ventricular beats. *C*, Regular sinus rhythm at a rate of 52 beats per minute.

Laboratory studies were all within normal limits, but a lateral roentgenogram of the chest showed an oval, retrocardiac mass which necessitated further investigation. An electrocardiogram showed regular sinus rhythm at a rate of 70 per minute and a left ventricular strain pattern.

Two days after an uneventful vaginal plastic repair, which had been done under general inhalation anesthesia, the patient suddenly developed a tachycardia at a rate of 166 beats per minute (Fig. 5,*A*); the blood pressure remained 120/80 mm. Hg. An intravenous drip of 8 mg. of levarterenol in 1,000 c.c. of 5 per cent glucose in water was started. The rate remained unchanged for 15 minutes and the blood pressure was stable at 120/80 mm. Hg. A second ampule of 8 mg.

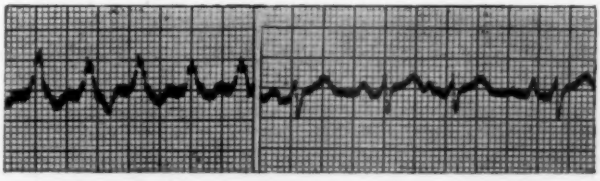
of levarterenol was added to the infusion and the pressure rose to 160/88 mm. Hg. At this point the rhythm reverted to regular sinus rhythm at a rate of 52 per minute (Fig. 5,*B* and *C*). The infusion was slowed and in a few minutes was completely halted.

The patient remained in regular sinus rhythm and was discharged shortly when further electrocardiograms showed no abnormalities. She is at present being studied with regard to the retrocardiac mass.

CASE 6.—A.T., a 67-year-old, white male, was admitted to the Medical Service of the Long Island College Hospital on May 16, 1954, complaining of severe precordial pain. Two days prior to admission, the patient had had an episode of severe precordial pain lasting 15 minutes; this had disappeared spontaneously. On the day of admission there was a recurrence of the pain, this time with radiation down the left arm; it persisted several hours before the patient finally presented himself for admission.

On admission the patient was found to be a well-developed, well-nourished, elderly male in moderate distress. The blood pressure was 122/80 mm. Hg, pulse 78 beats per minute. The heart was slightly enlarged to percussion, and the heart sounds were quite distant. Fine, moist râles were heard at both lung bases. The remainder of the physical examination was essentially negative. An electrocardiogram taken on admission revealed an extensive, acute, anterior wall myocardial infarct. The patient was given anticoagulants, sedation, and analgesia and was maintained at complete bed rest. The course was entirely uneventful for 10 days when severe dyspnea suddenly developed. The patient had Cheyne-Stokes respirations; the pulse was weak, thready, but not rapid; no auscultatory blood pressure could be obtained, and fine râles were again heard at both bases. An intravenous infusion of 1,000 c.c. of 5 per cent glucose in water containing 8 mg. of levarterenol was begun. At about the time the infusion was being started, it was noted that the pulse had risen to 185 beats per minute. An electrocardiogram revealed a supraventricular tachycardia at a rate of 185 beats per minute with intraventricular conduction damage (Fig. 6,*A*). Although it was felt that this was the diagnosis, the possibility of ventricular tachycardia cannot be ruled out. The rate of flow of the infusion was increased, and the blood pressure rose to 100/85 mm. Hg. Coincidental with this, there was prompt reversion to sinus rhythm with occasional auricular premature contractions (Fig. 6,*B*). These premature beats disappeared after several minutes. The subsequent course was complicated by several attacks of severe congestive failure which finally responded to digitalis and mercurial diuretics.

He was discharged after 7 weeks on digitalis and quinidine therapy.



A. *B.*

Fig. 6.—Case 6. A.T. *A*, Tachycardia at a rate of 185 beats per minute, probably supraventricular in origin with intraventricular conduction damage. *B*, Sinus rhythm at a rate of 100 beats per minute with premature auricular beats.

CASE 7.—R.R., a 41-year-old Puerto Rican, unemployed male, was brought to the Emergency Room of the Long Island College Hospital on Aug. 14, 1954, complaining of chest pain and palpitation of one hour's duration. The patient was well known to the Medical Service because of many previous admissions for attacks of paroxysmal tachycardia, presumably of ventricular origin. The previous episodes had responded to intravenous administration of 0.5 to 1.0 Gm. of procaine amide. The patient was discharged on high oral dosages of procaine amide or quinidine. These measures proved to be effective as long as the patient continued to take them as prescribed. He had been thoroughly investigated for organic etiology of the arrhythmia and a small diverticulum of the esophagus was discovered, the significance of which is questionable.

On this admission the patient was brought to the ward in acute distress, pallid and complaining of oppressive chest pain. The pulse was 220 beats per minute, the blood pressure 90/70

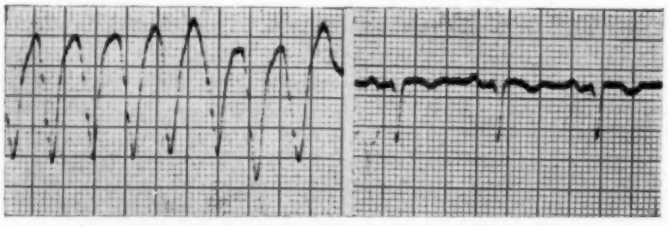
mm. Hg, and the respirations 40 per minute. The electrocardiogram was similar to former ones, being characteristic of ventricular tachycardia (Fig. 7,*A*). An infusion of 8 mg. of levarterenol in 1,000 c.c. of 5 per cent glucose in water was started intravenously, and the rhythm reverted to regular sinus rhythm at a rate of 94 beats per minute within several seconds after the infusion was begun (Fig. 7,*B*). Levarterenol was discontinued in one hour since the blood pressure became stabilized at 110/70 mm. Hg.

He was discharged on oral procaine amide and admonished to take it faithfully.

CASE 8.—Mrs. D.J., a 30-year-old white housewife with a history of rheumatic heart disease and mitral stenosis, was admitted to the Medical Service of the Long Island College Hospital on Oct. 30, 1954, because of chest pain and weakness. Immediately prior to her admission she had consulted a physician on the staff of this hospital because of these complaints. The pulse rate was 200 beats per minute and the blood pressure 80/60 mm. Hg. She was sent immediately to the Emergency Room for admission.

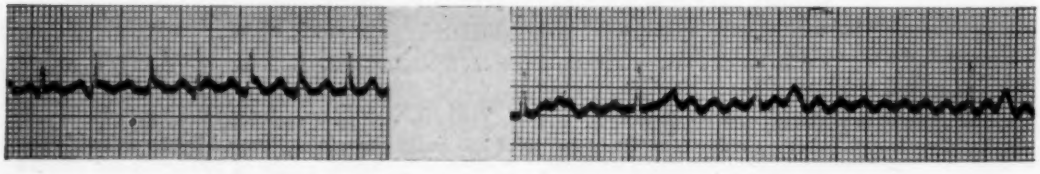
On arrival the blood pressure and pulse were unchanged; moist basilar râles were detected and there was minimal neck vein distention. An electrocardiogram revealed auricular flutter with a ventricular response of over 200 beats per minute (Fig. 8,*A*). An infusion of 1,000 c.c. of 5 per cent glucose in water with 8 mg. of levarterenol was begun. As the blood pressure rose to 160/90 mm. Hg, the ventricular rate slowed to 45 to 75 beats per minute and, at one point, the auricular rate also seemed to change (Fig. 8,*B*). However, almost immediately reversion to the original rate took place.

Subsequently the patient was restored to normal rhythm by means of oral digitoxin. Two days later embolization occurred to both the right femoral and left popliteal arteries. The patient is presently making an uneventful recovery following embolectomy.



A. *B.*

Fig. 7.—Case 7. R.R. *A*, Ventricular tachycardia at a rate of about 210 beats per minute. *B*, (Part of same continuous tracing) Normal sinus rhythm at a rate of 94 beats per minute.



A. *B.*

Fig. 8.—Case 8. D.S. *A*, Auricular flutter at ventricular rate of 200 beats per minute. *B*, Same auricular rate with marked slowing of ventricular rate to 45 to 75 beats per minute.

DISCUSSION

The mechanism by which levarterenol produces bradycardia in normal subjects, both animal and human, has been amply demonstrated.[1,4-8] Bradycardia induced by levarterenol was noted first in normal humans by Goldenberg and associates.[1] This effect had not been noticed at first in animals because investigations were conducted using isolated hearts[2] or anesthetized, atropinized

animals.[3] In these studies[2,3] levarterenol produced an increase in the heart rate although less marked than that caused by epinephrine.

Heymens and De Vleeschhouwer,[4] however, using intact dogs, noted the same bradycardic effect produced by levarterenol previously reported in humans by Goldenberg and associates.[1] They concluded that the bradycardic effect of levarterenol was a vagal influence caused by the stimulation of the aortic and carotid pressor receptors by the rise in systemic arterial pressure. They noted that there seemed to be no effect on the vagal cardioinhibitory center in the midbrain.

Goldenberg and associates[1] carefully studied eight normal human subjects who were receiving intravenous infusions of levarterenol. The following effects were noted: (1) There was no change or there was a slight decrease in cardiac output. (2) In all cases the systolic arterial pressure rose; the mean pressure also rose in all but two cases (those receiving the smallest doses); the diastolic pressure also rose. (3) The peripheral resistance rose in five of the eight cases. (4) The pulmonic arterial pressure rose in all cases. (5) The pulse rate fell significantly in all but one case. This bradycardia was abolished by atropine in three cases and was thus considered to be of vagal origin.

Barcroft and Konzett[5,6] compared the actions of epinephrine and levarterenol on the human heart rate. They found that at comparative dosage levels levarterenol caused bradycardia and epinephrine caused tachycardia. In seven normal human subjects, aged 20 to 45, epinephrine increased the pulse rate from 12 to 45 beats per minute, while levarterenol caused a drop in pulse rate of 6 to 27 beats per minute. In one case the levarterenol caused an increase of 7 beats per minute, but this was abolished by an increase in dosage. The authors, noting that the bradycardia occurred only when the blood pressure rose, concluded that the slowing of the pulse was secondary to levarterenol's pressor effect.

In twenty-six normal persons, Sutton and associates[7] noted that irrespective of the dosage used, the effect of the drug consisted only of a rise in systemic arterial pressure and a slowing of the heart rate.

Von Euler[8] also draws attention to the bradycardic effect of levarterenol resulting from a reflex vagal action initiated by stretch receptors in the carotid sinus and aorta.

Recently, there have been reports in the literature[9-11] noting the use of a synthetic pressor amine—Methoxamine hydrochloride (beta- [2,5 dimethoxyphenyl] beta-hydroxy-isopropyl amine)—in the treatment of paroxysmal supraventricular tachycardias. The present results are similar to those described with Methoxamine hydrochloride. In no case was an attack terminated until a substantial rise in blood pressure had been obtained.

In the light of these findings, the action of levarterenol in terminating attacks of paroxysmal tachycardia is similar to the simpler methods of vagal stimulation, such as carotid sinus pressure, but more profound. The suggestion that the drug acts through vagal stimulation is also supported by the observation in the patient showing auricular flutter. The temporary slowing which took place is similar to the effect of carotid sinus pressure in cases of au-

ricular flutter. In patients who had received digitalis before the levarterenol was administered (Cases 2 and 3), the same sequence of events was observed—a reversion to normal rhythm or a substantial slowing as the blood pressure rose. It might be thought that digitalis produced the cessation of the attack, but in Case 2 sufficient time did not elapse before reversion to normal rhythm for digitalis to play any part. It is extremely doubtful in Case 3 whether any marked digitalis effect would be present so shortly after its administration.

The authors feel that levarterenol is a safe, efficacious means of treating paroxysmal tachycardia. Even in the instances in which it failed, no deleterious effects were noted. The transient ventricular arrhythmias seen in Cases 3, 4, and 5 are observed sometimes in spontaneous reversions and in those induced by other drugs.[12] They are considered escape rhythms and disappear rapidly without therapy. Although the duration of the ventricular arrhythmia is usually very brief, when cases of paroxysmal tachycardia are to be treated with levarterenol it might be well to have a solution of procaine amide available for intravenous injection if the ventricular arrhythmia should persist. Should the blood pressure fall after the injection of procaine amide, the levarterenol solution can be used to raise it.[13,14] It should be noted, however, that in this series of cases it was not necessary to use procaine amide on any patient.

The cases in which the drug failed were of two classes: those in which no rise in blood pressure could be obtained or those in which myocardial infarction, or other severe heart disease, complicated the picture.

The authors feel that levarterenol should be tried in cases of paroxysmal tachycardia in which the blood pressure is normal or low. It should be administered to patients with paroxysmal tachycardia under direct electrocardiographic control. The blood pressure should be taken continually to avoid dangerous hypertension. The hypertensive effect can easily be controlled by regulating the speed of the infusion. If no effect on the pulse rate is noted after the systolic pressure has been raised to normotensive or slightly hypertensive levels, digitalis, quinidine, or procaine amide therapy can be instituted immediately.

It should be noted that levarterenol is not recommended in ventricular tachycardia except as an ancillary agent used to correct the hypotension associated with the arrhythmia. In the case cited above (No. 7) the reversion to normal rhythm occurred while the shock was being corrected preparatory to procaine amide therapy.

SUMMARY

1. Six cases of supraventricular paroxysmal tachycardia and one case of ventricular tachycardia are presented in which the administration of levarterenol intravenously caused termination of the attack. In one case of auricular flutter the rate was slowed temporarily but the abnormal rhythm persisted.

2. Administration of the drug was only successful when it elevated the blood pressure to approximately normal levels.

3. It is suggested that levarterenol acts in those cases in which it causes reversion to normal rhythm by elevating the blood pressure. This stimulates

receptors in the aorta and carotid sinus, causing reflex stimulation of the vagus. The profound vagal stimulation thus induced causes cessation of the attack.

SUMMARIO IN INTERLINGUA

Le autores presenta 6 casos in que tachycardia supraventricular paroxysmal esseva convertite in rhythmo sinusal normal per medio de bitartrato de levarterenol. In plus levarterenol serviva a converter un caso de tachycardia ventricular in rhythmo sinusal e a relentar un caso de flutter auricular.

Le autores opina que le termination de un attacco de tachycardia supraventricular paroxysmal per medio de levarterenol es un effecto secundari al stimulation vagal causate per le augmento del pression sanguinee in le receptores del sinuses carotide. Es presentate datos in supporto de iste opinion.

ADDENDUM

In support of the thesis that levarterenol acts through stimulation of the carotid sinus, these studies were made at the Long Island College Hospital on a patient suffering from supraventricular tachycardia at a rate of 260. Levarterenol was administered and produced profound alteration in the ventricular complexes without relief of tachycardia. After the levarterenol wore off, stimulation of either the right or left carotid sinus produced exactly the same changes in ventricular complexes.

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Clinical Reports

EBSTEIN'S ANOMALY OF THE TRICUSPID VALVE: ANGIOCARDIOGRAPHIC DIAGNOSIS

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WASHINGTON, D. C.

THE congenital anomaly first described by Ebstein[1] consists of a displacement of the tricuspid valve towards the cardiac apex so that the proximal portion of the original right ventricle becomes atrialized and the distal portion functioning as ventricle becomes reduced. The characteristic division of the right ventricle into proximal and distal portions was first demonstrated angiocardiographically by Soloff and associates.[2] Blacket and his associates[3] described a similar angiocardiogram. This is the report of another case with this diagnostic feature.

CASE REPORT

A 26-year-old law student was admitted to George Washington University Hospital, April 18, 1951, because of pain in the right upper part of the abdomen and in the angle of the right scapula of two days' duration. Two weeks before he had had a mild upper respiratory infection. He had had no previous serious illness.

The abnormal *physical signs* were limited to the cardiovascular system. The apical rate was 180/min. and irregular during the first hospital day, slowing to 90/min. by the Valsalva maneuver. There was no cyanosis or clubbing and no evidence of congestive heart failure. A prominent thrust was palpable along the left sternal border from the second to the fourth intercostal spaces. The pulmonic second sound was intensified, distinctly split, and louder than the aortic second sound. The first and second sounds at the apex were equal. There was a Grade 2, localized, soft systolic murmur at the apex, and a low-pitched systolic murmur in the left parasternal region maximal in the third intercostal space. The latter murmur varied considerably with respiration and at times sounded like a click. There were no diastolic murmurs. The blood pressure was 130/85 mm. Hg. During the first two days in the hospital the liver edge was palpable about 2 cm. below the right costal margin, and the liver was tender; subsequently there was no liver enlargement or tenderness. The ocular fundi were normal.

Electrocardiograms showed atrial flutter with varying A-V block. Regular sinus rhythm was restored by means of lanatoside C administered intravenously, and the electrocardiogram then showed incomplete right bundle branch block (Fig. 1). The latter persisted in electrocardiograms fourteen months after the initial observation.

Fluoroscopy and roentgenograms of the chest revealed cardiomegaly with a peculiar rounded prominence above the apex in the posteroanterior view (Fig. 2). The pulmonary vessels appeared normal, and their pulsations were normal. The retrocardiac space was clear, and there was no abnormal displacement of the barium-filled esophagus. In the left anterior oblique view the

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Received for publication Dec. 3, 1954.

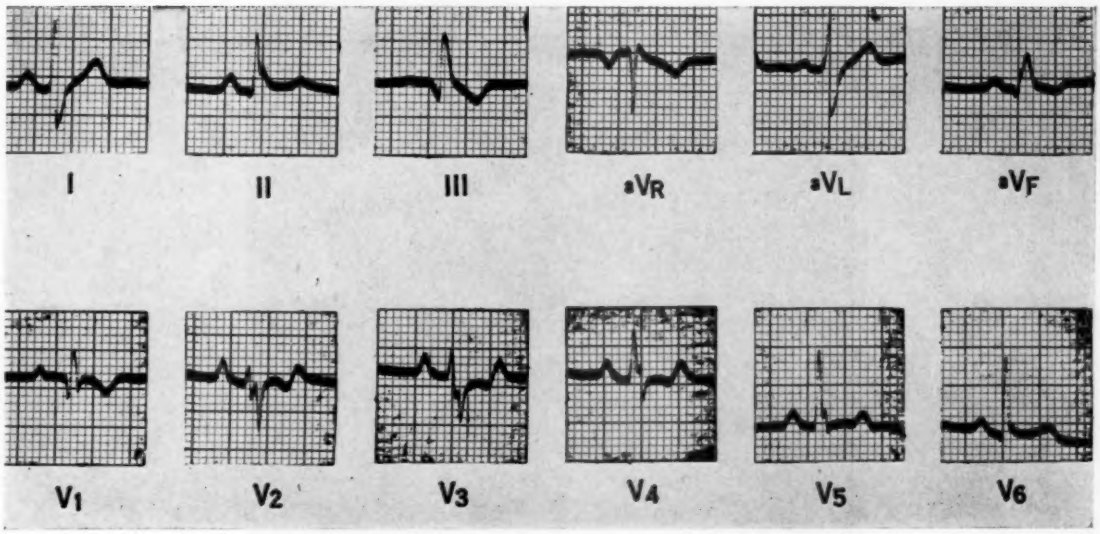


Fig. 1.—Electrocardiogram.

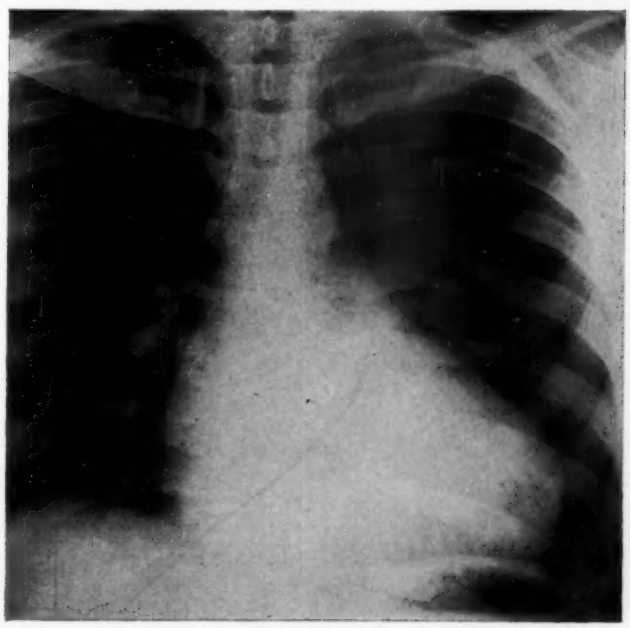
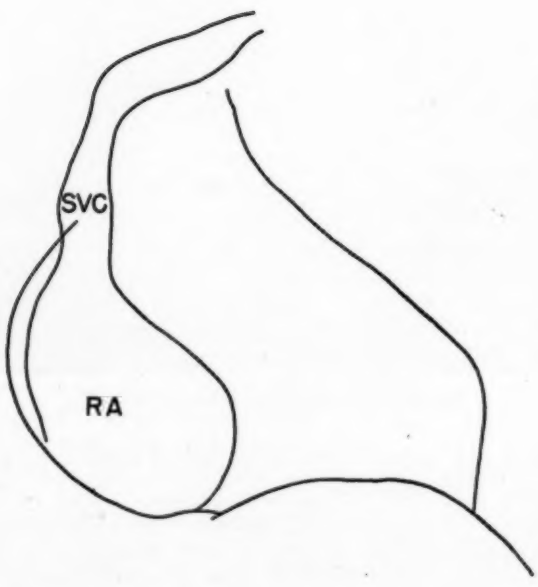


Fig. 2.—Conventional roentgenogram.

ventricular mass extended well beyond the anterior spinal border. The roentgenologist's impression was possible ventricular aneurysm.

Angiocardiograms were done on three different occasions. Immediately after the injection of radiopaque material an enlarged right atrium was demonstrated (Fig. 3). The entire cardiac area was rapidly opacified leaving only a thin wall on the left cardiac border. There was a peculiar deep notch on the inferior border far over toward the right, demarcating a pouch from the remainder of the heart (Fig. 4). The notch and pouch were demonstrable only during fortuitous exposures, probably related to the phase of the cardiac cycle. On one of the three series of angiocardiograms the notch was absent. In the second series (Fig. 4) it was present in the first exposure

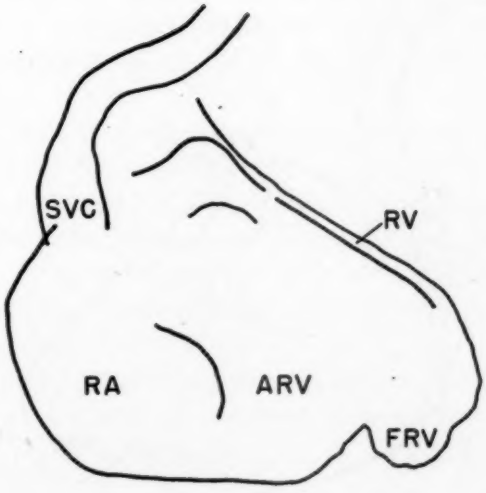
A.



B.

Fig. 3.—Angiocardiogram(*A*) and diagram of angiocardiogram(*B*) immediately after intravenous injection of 70 per cent Diodrast. RA = right atrium; SVC = superior vena cava.

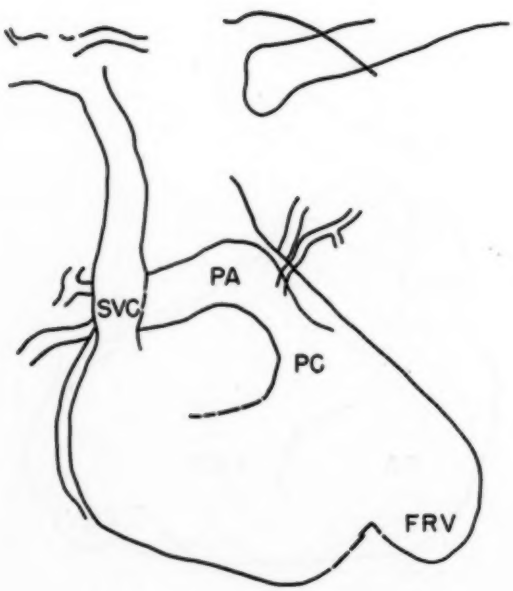
A.



B.

Fig. 4.—Angiocardiogram(*A*) and diagram of angiocardiogram(*B*) approximately one second after intravenous injection of 70 per cent Diodrast. ARV = atrialized portion of right ventricle; FRV = functioning portion of right ventricle; RA = right atrium; RV = wall of right ventricle; SVC = superior vena cava.

A.



B.

Fig. 5.—Angiocardiogram(*A*) and diagram of angiocardiogram(*B*) approximately four seconds after intravenous injection of 70 per cent Diodrast. FRV = functioning portion of right ventricle; PA = main pulmonary artery; PC = pulmonary conus; SVC = superior vena cava.

approximately one second after injection, but not in subsequent exposures at 2½, 4, 5½ seconds even though the latter still demonstrated definite opacification of the right side of the heart. In the third series the first two exposures did not show the notch, whereas the third and fourth did (Fig. 5). The pulmonary conus was far over on the right (Fig. 5), and the pulmonary arteries were faintly visualized. The opacification of the entire cardiac area was still present at 7 to 8½ seconds, when a normal left atrium was visualized as a superimposed density. The aorta was visualized, but the left ventricle was not delineated. There was no evidence of right-to-left shunt.

Cardiac catherization was carried out after the angiocardiograms had been studied, but before their significance was appreciated. (Several deaths following catheterization in Ebstein's anomaly have been reported.)[3,9] An attempt was made to pass the catheter into the tip of the pouch visualized in the angiocardiograms without success. The oxygen saturations and the pressures in the right atrium, the right ventricle and the pulmonary artery were normal.

By October, 1954, there had apparently been no recurrences of cardiac arrhythmia although occasionally when he is very fatigued the patient feels a "strong, rapid heart beat." He pursues an active life and continues to study law at night.

COMMENT

Since a patent foramen ovale may or may not be associated with Ebstein's anomaly[4] the angiocardiographic picture may vary. Most characteristic of the anomaly is the separation of the functioning portion of right ventricle from the proximal portion. It is important to recognize that this separation may be apparent only during a part of the cardiac cycle, probably most clearly at the height of systole. Angiocardiographic technique which permits exposures at predetermined times of the cardiac cycle or many exposures at frequent intervals is most reliable.

The angiocardiographic picture would seem to be pathognomonic, although Goodwin and associates[5] believe that extreme right atrial enlargement due to severe pulmonary stenosis may simulate it by displacing the normal atrioventricular notch toward the left. This confusion should not arise when the original atrial chamber is outlined as in the case of Soloff and his associates[2] and in this case. The notch is seen to be far removed from the margin of this chamber.

The other angiocardiographic characteristics are (1) enlarged right atrium, (2) rapid opacification of the entire cardiac shadow in the posteroanterior view leaving a thin wall of right ventricle on the left border, (3) abnormal persistence of opacification of the right atrium and ventricle, and (4) no or faint visualization of pulmonary arteries, left atrium, left ventricle and aorta, except that this may be altered by an associated right-to-left shunt. Some or all of these have been observed in proved or presumed cases.[2-9]

The diagnosis is of practical significance in spite of the rarity of the condition, because Ebstein's anomaly may be confused with tetralogy of Fallot,[4,5] pulmonary stenosis,[4,5] and tricuspid atresia.[5]

SUMMARY

Angiocardiograms are described which are believed to be characteristic of Ebstein's anomaly of the tricuspid valve, and the other clinical features in one case are presented. The division of the right ventricle into a proximal atrialized

portion and a distal functioning portion is demonstrable by angiocardiography in this case.

SUMMARIO IN INTERLINGUA

Es describite angiocardiogrammas que nos considera como characteristic del anomalia Ebstein del valvula tricuspide. Altere observationes clinic facite in un caso de nostre practica es presentate. In illo medios angiocardiographic permitte le demonstration del division del ventriculo dextere in (1) un portion proximal que es atrialisate e (2) un portion distal que continua functionar como ventriculo.

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Announcements

The American College of Cardiology will hold its fourth interim meeting at the Hotel Claridge, Memphis, Tenn., November 10-12, 1955. The scientific program will feature symposia on rheumatic fever, rheumatic heart disease, and vascular surgery. It will include speakers from the medical schools of Vanderbilt and Emory Universities and the Universities of Tennessee, Mississippi, Arkansas, and Kansas City, as well as the National Children's Cardiac Hospital of Miami. In addition to the scientific sessions, there will be a social program, with a banquet and an evening cruise up the Mississippi on a river boat. There will be a Dixie Band and a Southern barbecue on the cruise. Further information regarding the program may be obtained from the secretary of the College, Dr. Philip Reichert, American College of Cardiology, Empire State Building, New York 1, N. Y.

The Ninth Annual Meeting of the American Society for the Study of Arteriosclerosis will be held November 6 and 7, 1955, (Sunday and Monday) at the Sheraton Hotel, Chicago, Illinois. Program and Abstracts of 69 papers will be published in the October issue of *Circulation*.

Book Reviews

FLUOROSCOPY IN DIAGNOSTIC ROENTGENOLOGY. By Otto Deutschberger, M.D., Philadelphia, 1955, W. B. Saunders Company.

This volume is devoted to the clinical use of the fluoroscope in the diagnosis of disease. The first section of the book is devoted to a discussion of the technical aspects of fluoroscopy, including an excellent section on its hazards. This section in itself is a distinct contribution to the knowledge of the clinician who utilizes the fluoroscope in clinical practice. Another portion is devoted to a discussion of the electronically amplified fluoroscopic image, which is a technical advance of considerable importance.

While there are sections on examination of the head, neck, and extremities, the major portion of the volume in the second section is devoted to diagnostic findings in examination of the heart and lungs, of the abdomen, and of the genitourinary tract. The photographs of this book are positive prints showing the radiopaque areas dark and the transparencies bright. This gives an appearance similar to the images as seen on the fluoroscopic screen. As a practical matter, it should be pointed out that the images seen fluoroscopically will not be as clearly defined, in many or most instances, as the roentgenograms used in the illustrations would indicate.

The section on fluoroscopy of the lungs is well written and includes much information about the physiologic variations in the appearance of the heart and lungs, under various conditions in normal circumstances. While the discussion of pathologic lesions of the lungs is an excellent one, the reviewer feels that the limitations of fluoroscopy are marked in the diagnosis of smaller lesions of the lungs. Normal and abnormal dynamic changes in the process of ventilation are well described in this section.

The section on fluoroscopic examination of the heart is an excellent one, and the descriptions of the heart, under both normal and disease conditions, are well documented by numerous roentgenographic reproductions and outline drawings. In the opinion of the reviewer, the author has covered this field of cardiac disease well, and it is in this particular field that the reviewer personally feels fluoroscopy is of the greatest value. The section on examination of the abdomen is fairly complete and well written, including the use of contrast material in studying the gastrointestinal tract. At the end of each of the sections, there is a fairly extensive bibliography which enhances the value of this textbook as a reference work. It is a well written treatise and will be of interest not only to radiologists, but to cardiologists and internists, generally.

H.E.H.

ANGINA PECTORIS. By W. H. Hauss, M.D., Stuttgart, 1954, Georg Thieme, 394 pages, 127 figures, 23 tables.

Although angina pectoris, as a clinical syndrome, may occur in various pathologic conditions, coronary heart disease is by far the most common, and is therefore the essential topic of the book, duplicating to a large extent available texts.

There is a brief, but interesting historical introduction, followed by chapters on etiology, clinical picture, pathologic-physiologic problems, differential diagnosis, prognosis, and therapy of angina pectoris with and without myocardial infarction.

Electrocardiography, as the most important diagnostic method, takes a major part of the content. All tracings were taken with a three-channel machine which seems to be standard equipment in German hospitals. In addition to the standard leads and V_1 to V_6, the Nehb leads are taken instead of the unipolar limb leads. This seems to be justified because the Nehb triangle lies in a different plane from the standard leads, while standard and unipolar-limb leads are in the frontal plane. In some cases, indeed, the changes in the Nehb leads are more impressive than those in the standard leads and V_1 to V_6, but few, if any, cases show abnormal deviations in the Nehb leads alone.

One can agree with the statement that the differentiation between a large and a small infarct is clinically more important than the differentiation of the infarct location, but hardly with the criteria advanced for this purpose, which are, in general, based on the somewhat naive concept of a parallelism between the size of the infarct and the extent of electrocardiographic changes. A small infarct, for instance, is diagnosed when only T-wave changes but no QRS changes occur.

It is recognized that myocardial infarct may produce T inversion without QRS changes, but it is a different matter to diagnose outright an infarct from T changes (often reversible within a few days) alone. While the transition between infarct and coronary insufficiency is fluid, it seems that the electrocardiographic changes are used mainly to corroborate the clinical impression, i.e., the author reads into the electrocardiogram what he knows about the patient.

With the author's criteria, it is impossible to differentiate an infarct from coronary insufficiency, myocarditis, or pericarditis. Hauss suggests that the S-T elevation in acute myocardial infarction starts on the descending limb of the R wave, and in pericarditis after the S wave, but curiously enough, this pattern is illustrated by a case of posterior wall infarct and not pericarditis.

Interesting material mostly in the form of individual case reports is presented on the general relationship of myocardial infarct or angina pectoris to environmental and constitutional factors, and on interaction with other types of pathology. Hypoglycemia, chest injury, allergic reaction, diseases of the intestinal organs, diaphragm, and the vertebrae, psychic trauma, etc., may in the presence of coronary disease be responsible for the development of a myocardial infarction. The possible mechanisms involved in such interaction are discussed on the basis of the available experimental material.

That such causal relationships exist is of interest, and therefore the collection of such information is valuable. However, the presentation is not unbiased and not balanced. While the author goes to some length to show that apparently remote factors may be occasionally involved in the production of an infarct, the relationship between coronary disease and blood lipids is denied in spite of the large and impressive literature, which is essentially ignored (p. 74). The author devotes considerably more space to hypoglycemia than to blood lipids.

In the discussion of prognosis and of complications in myocardial infarction, interesting material from the University Hospital in Frankfurt corroborates the much larger material published in the American literature on the evaluation of anticoagulant therapy. Of interest is the treatment of shock in infarct with bilateral carotid-sinus block.

One misses a chapter on functional tests (exercise, anoxia, meal) which should have a place in a book on angina pectoris.

The book cannot be recommended as an introduction for a medical student or for the general practitioner, but the informed cardiologist will find interesting data on some aspects which are often by-passed in the American cardiologic literature. The quality of the illustrations is excellent, and there is a large bibliography of 35 pages.

E.S.

DAS TRANSVERSALE SCHICHTVERFAHREN. By Alfred Gebauer, M.D., and Alfred Schanen, M.D., Stuttgart, 1955, Georg Thieme, 313 pages.

The author states in the foreword that this is the second book devoted to transverse tomography. (The first was written by Vallebona in Italy.)

This work is technically very beautiful. It is primarily a technical handbook for the use of x-ray departments. The method is relatively limited in value in the differential diagnosis of heart disease, some forty pages are devoted to the heart and the large blood vessels.

The book can be warmly recommended for the student who wishes to develop this approach to the study of pathology of the thoracic cavity.

J.J.